CONTENTS

The American Journal of Medicine

VOL. III AUGUST, 1947 No. 2

Editorial

Clinical Studies

Contents continued on page 5

liver disorders

cirrhosis
fat infiltration
functional impairment
toxic hepatitis
infectious hepatitis

methischol

(pronounced meth' is kol)

A synergistic combination of METHIONINE, CHOLINE and INOSITOL in a LIVER-VITAMIN B COMPLEX BASE . . . lipotropic substances which favor the transport of fat from the liver to the fat depots of the body . . . for prophylaxis, retardation and specific therapy in reparable liver damage.

each tablespoonful contains:

dl-Methionine ..... 333 mg.
Choline ..... 250 mg.
Inositol ..... 176 mg.
together with the natural B complex from 11.2 grams of liver.

Supplied in bottles of 8 oz. and 16 oz. syrup.

advantages of **methischol**

1. three efficient lipotropic agents.
2. natural B complex from liver.
3. essential, readily utilized METHIONINE.
4. well tolerated, non-toxic, convenient.

Detailed literature and sample.

u. s. vitamin corporation
casimir funk labs., inc. (affiliate)
250 east 43rd street • new york 17, n. y.

CONTENTS

The American Journal of Medicine

VOL. III AUGUST, 1947 NO. 2

Contents continued from page 3

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Change of address must reach us by the 15th of the month preceding month of issue.

PREPARATION OF MANUSCRIPTS

Text. Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

Illustrations. Illustrations must be in the form of glossy prints or drawings in black ink (*never* in blue). On the back of each illustration the figure number, author's name and an indication of the top of the picture should be given. Legends for illustrations are to be typewritten in a single list, with numbers corresponding to those on the photographs and drawings. Please do not attach legends to the pictures themselves.

Bibliographies. Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

The subscription price of THE AMERICAN JOURNAL OF MEDICINE, is $10.00 per year in advance in the United States; $12.00 in Canada and foreign countries. Current single numbers $2.00. All Special Numbers $4.00. Prices for such back numbers as are available will be quoted on request.

Address all correspondence to

The American Journal of Medicine · 49 West 45th Street · New York 19

"Don't try to bribe me—I want D-P-T★"

Maybe babies don't cry for them—but they will be better protected with Cutter's combined vaccines. And run less risk of painful reactions, too! Here's why:

1. ***Phase I pertussis organisms*** for D-P-T are *grown on human blood* —to assure high antigenicity of organisms, and to avoid the danger of anaphylactic shock from heterologous animal protein.
2. ***Diphtheria and tetanus toxoids*** are so *purified* that every cc. contains well over a single human dose each.
3. ***Concentration of toxoids***—plus 40 billion Phase I pertussis organisms per cc.—permit a dosage schedule of only 0.5 cc., 1 cc., 1cc.

You'll find advantages in another Cutter product, too—D-P-T *(Alhydrox)*. It provides higher immunity levels than alum precipitated vaccines. Cuts to a minimum such side reactions as persistent nodules and sterile abscesses. And presents less pain on injection because of a more physiologically normal pH.

Choose D-P-T—Plain or Alhydrox—you'll appreciate them in your practice.

★ *Cutter's brand of combined diphtheria, pertussis and tetanus antigens.*

Cutter Laboratories, Berkeley 1, California
Chicago • New York

Need an "answer book" for parents in your practice? Write for gift copies of Cutter's new booklet— "How to Prevent Diseases of Children."

CUTTER

Fine Biologicals and Pharmaceutical Specialties

CALM

n Essential Hypertension
nd Angina Pectoris

MAXITATE

REG. U. S. PAT. OFF.

MANNITOL HEXANITRATE, STRASENBURGH

Pioneered by STRASENBURGH *Research*

The Original Stabilized Formula

Gradual and *prolonged* vasodilation... lasting 5 to 6 hours. Uniformly dependable action.

PACKAGE DATA:

Available in bottles of 100 and 1000 tablets.

Maxitate ¼ gr. (white) Not Scored
Maxitate ½ gr. (white) Scored
Maxitate ½ gr. with Phenobarbital ¼ gr. (blue) Scored
Maxitate ½ gr. with Phenobarbital ½ gr. (pink) Scored
Maxitate ½ gr. with Nitroglycerin 1/100 gr. (violet) Scored

R. J. STRASENBURGH Co.

PHARMACEUTICAL CHEMISTS SINCE 1886

ROCHESTER 4, NEW YORK

The combination of — **Sulfamerazine *Microcrystalline*..1.5 Gm. (22 gr.)**
Sulfadiazine *Microcrystalline*....1.5 Gm. (22 gr.)

is presented in Mer-Diazine. Equal parts of sulfamerazine and sulfadiazine have been found by Flippin et al* to lead "to a markedly decreased incidence of crystalluria compared with that observed when either compound was administered singly . . . The use of sulfonamide mixtures avoids certain disadvantages associated with the administration of sodium bicarbonate . . ."

Liquoid Mer-Diazine — presents a palatable, homogenized suspension of these two sulfonamides. The microcrystalline form in which the drugs are present assures the most rapid absorption; slow excretion of sulfamerazine makes maintenance of a suitable blood level relatively simple; both sulfas penetrate readily into ascitic, pleural and cerebrospinal fluids.
Liquoid Mer-Diazine provides convenience in administration—particularly useful in pediatrics.
Warning: Sulfadiazine and Sulfamerazine may cause toxic reactions.

Available in 4 fl. oz. and pint bottles. Samples on request.

*Flippin, H. F. and Reinhold, J. G.: Ann. Int. Med., 25:433 (Sept.) 1946.

McNEIL
LABORATORIES, INC., PHILADELPHIA 32, PENNSYLVANIA

PABA

SODIUM

PARA-AMINOBENZOIC ACID
SODIUM SALT

for rickettsial infections

Now available in all prescription pharmacies

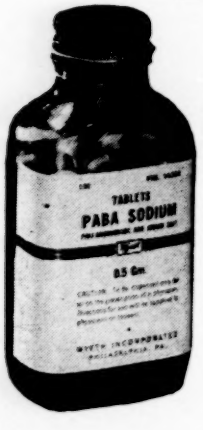
Paba shortens the course and moderates the symptoms of

Rocky Mountain spotted fever[1-5]
Flea-borne (endemic or murine) typhus[6-8]
Louse-borne (epidemic or European) typhus[9,10]
Tsutsugamushi disease (scrub typhus)[11,12]

Paba seems to be as specifically effective against rickettsias as sulfonamides or penicillin against susceptible bacteria.

Prophylactic dose: 2-4 Gm. daily, depending on age.
Therapeutic dose: 4-6 Gm. initially, followed by 2-3 Gm. every two hours.

1. J.A.M.A. 129:1160, 1945.
2. Delaware State M.J. 18:104, 1946.
3. J.A.M.A. 131:1364, 1946.
4. J.A.M.A. 132:911, 1946.
5. J.Pediat. 30:72, 1947.
6. Bol. Asoc. méd. de Puerto Rico 38: 189, 1946.
7. J.A.M.A. 131:1114, 1946.
8. Texas State J.Med. 42:314, 1946.
9. J.A.M.A. 126:349, 1944.
10. J. Lancet 67:60, 1947.
11. J.A.M.A. 131:280, 1946.
12. Lancet 2:96, 1946.



PABA

PARA-AMINOBENZOIC ACID
SODIUM SALT

0.5 Gm. tablets—bottles of 100

Wyeth

WYETH INCORPORATED • PHILADELPHIA 3, PA.

FOLIC ACID... *a bone marrow stimulant... is available now in* SQUIBB *prescription vitamin mixtures*

THERAPEUTIC FORMULA SQUIBB *and* **SPECIAL FORMULA SQUIBB**

... two widely prescribed vitamin preparations – *are now available with folic acid* (*the* MODIFIED *formulas*) *and without folic acid.* The new modified formulas containing folic acid are given below. The other formulas remain unchanged and are identical with those below except for the absence of folic acid.

for therapy ... THERAPEUTIC FORMULA—*MODIFIED*

VITAMIN CAPSULES

each capsule contains:

Vitamin A	25,000 units
Vitamin D	1,000 units
Thiamine HCl	10 mg.
Riboflavin	5 mg.
Niacinamide	150 mg.
Ascorbic Acid	150 mg.
Folic Acid	5 mg.

For *therapeutic* use in mixed vitamin deficiencies associated with certain macrocytic anemias – one or two capsules daily.

for prophylaxis ... SPECIAL FORMULA—*MODIFIED*

VITAMIN CAPSULES

each capsule contains:

Vitamin A	5,000 units
Vitamin D	800 units
Thiamine HCl	3 mg.
Riboflavin	3 mg.
Niacinamide	20 mg.
Ascorbic Acid	75 mg.
Folic Acid	1 mg.

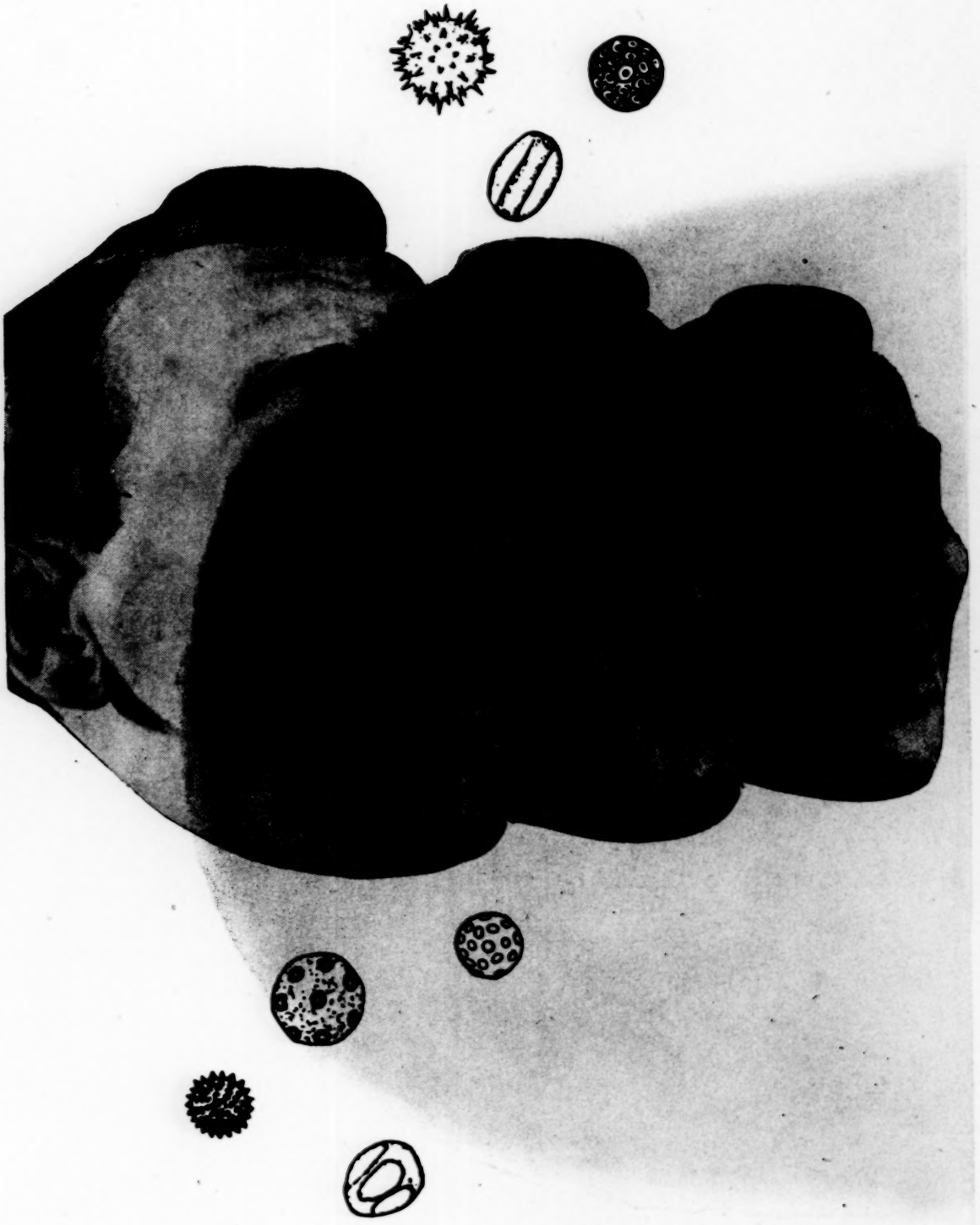
For the *prevention* of deficiencies in vitamins – one capsule daily.

Bottles of 100 and 1000

Also available: Folic Acid Squibb—Tablets of 5 mg., boxes of 25 and 100

SQUIBB

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

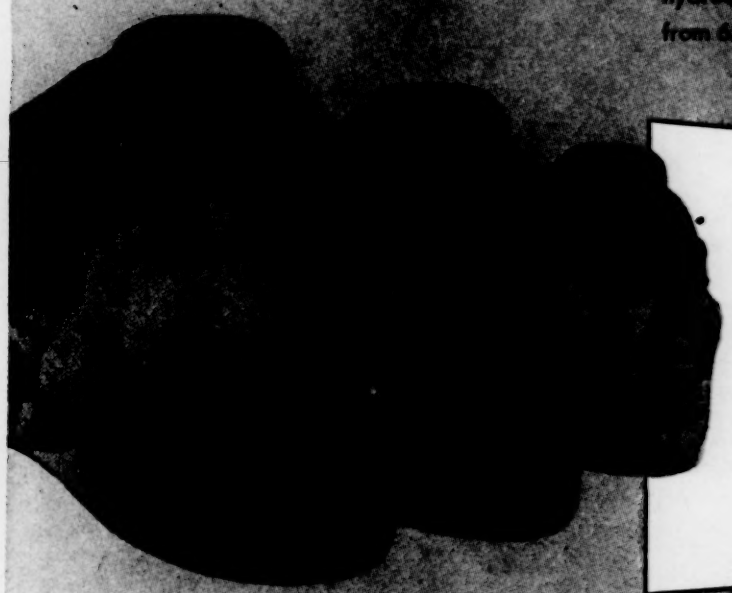


Pyribenzamine

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY

highly successful in treating hay fever...

Council-accepted Pyribenzamine hydrochloride has been reported to give from 65[1] to 82[2] per cent relief in hay fever.



POLLEN SEASON COMING

Among other conditions which Pyribenzamine benefits are vasomotor rhinitis, urticarial dermatoses, atopic dermatitis, penicillin and sulfonamide allergic reactions, and asthma. The relatively low frequency and intensity of side effects with Pyribenzamine permit its use in the previously intolerant or refractory patient.[2]

[1] Chobot, E.: J. Allergy, Jan. 1947.
[2] Feinberg, S. M.: J.A.M.A. 132:702 (Nov. 23) 1946.

PYRIBENZAMINE ® (brand of tripelennamine)

For further information and sample write Professional Service Division.

CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, NEW JERSEY

WHENEVER NUTRIENT INTAKE MUST BE AUGMENTED

The occasion frequently arises when the intake of all essential nutrients must be increased, as in general undernutrition, following recovery from infectious diseases and surgical trauma, and during periods of anorexia when food consumption is curtailed.

In the general management of these conditions, the dietary supplement made by mixing Ovaltine with milk can find wide applicability. Delicious in taste, it is enjoyed by all patients, young and old. Its low curd tension and easy digestibility impose no added gastrointestinal burden on the patient. This nutritious food drink supplies all the nutrients considered essential for a dietary supplement: biologically adequate protein, readily utilized carbohydrate, easily emulsified fat, B-complex and other vitamins including ascorbic acid, and essential minerals. The recommended three glassfuls daily virtually assures normal nutrient intake when taken in conjunction with even a fair or average diet.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B_1	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	2.00 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

Try this Yourself,

Doctor...

Rare is the person who does not enjoy a piece or two of candy at the end of a meal. The satisfying goodness of candy creates an aura of well-being which, post-prandially, is conducive to good digestion of the meal just eaten.

That candy has a worth-while place in the dietary is evident from the foods with which most candies are made—eggs, butter, milk, fruits and nuts. To the extent these foods are present, candies contribute valuable protein, B complex vitamins, and minerals.

In the sickroom, candies serve a double purpose. They frequently are eaten when many foods are refused because of anorexia, and serve to provide high caloric value in concentrated form. Of equal significance, convalescent patients usually experience a distinctly beneficial psychic lift from a tasty piece or two of candy.

These unique advantages of candies more than justify their inclusion in the daily dietary, not only of adults, but of children as well.

COUNCIL ON CANDY OF THE NATIONAL CONFECTIONERS ASSOCIATION

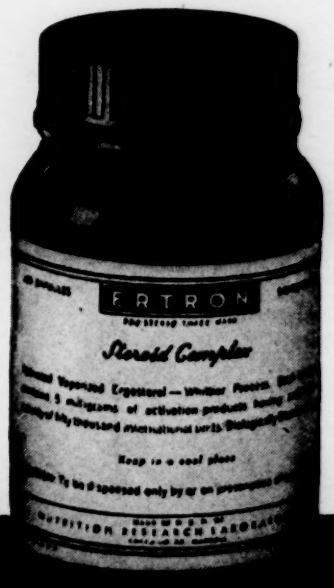
1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS

HAVE YOU A STUBBORN ARTHRITIC CASE?

Have you fully investigated the literature on Ertron-Steroid Therapy in Arthritis? Reprints of important articles and clinical reports are available, affording a valuable contribution to your files.

ERTRON*

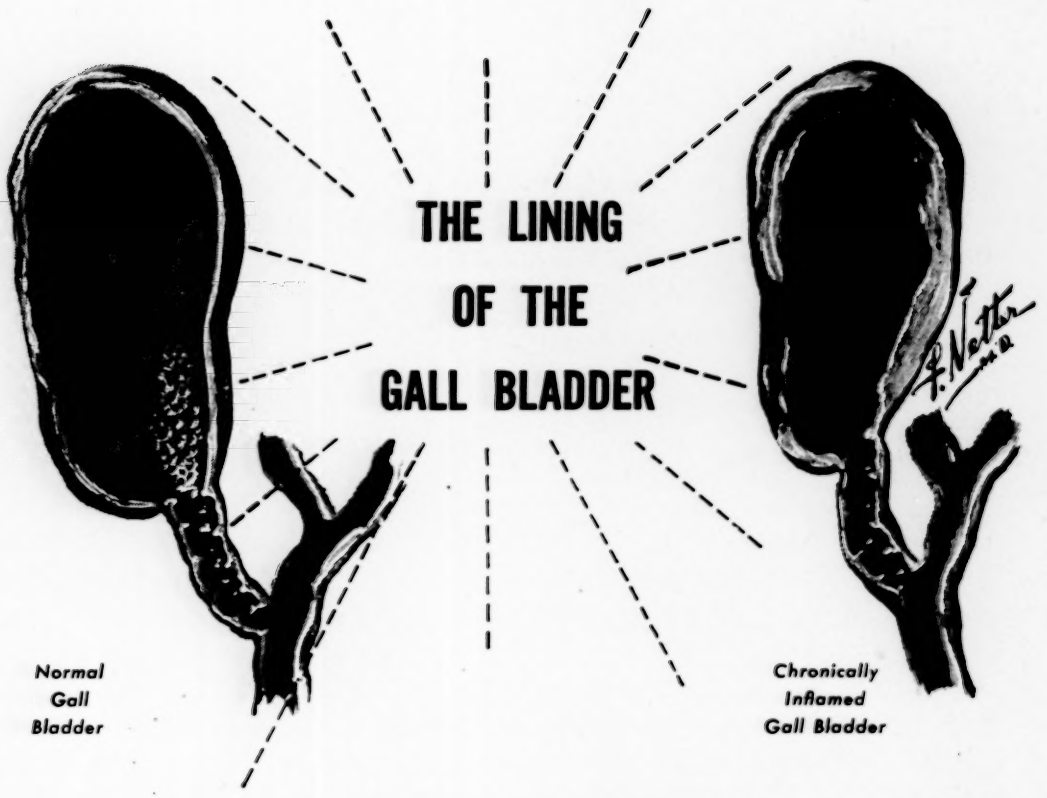
Steroid Complex, Whittier



*Reg. U. S. Patent Office

NUTRITION RESEARCH LABORATORIES

CHICAGO



The normal gall bladder lining is a soft, delicate mucosal layer characterized by numerous minute pockets over its surface. When inflamed it becomes thickened and coarse to a variable degree. Biliary stasis is believed to be a major factor in inciting a catarrhal inflammation which, with secondary infection, may progress to a more virulent cholecystitis, with or without cholelithiasis.

DEHYDROCHOLIC ACID *ARMOUR* is a powerful hydrocholagogue and choleretic. It induces a copious outflow of thin, watery bile which is low in total solids . . . in effect, a physiologic "flushing-out" of the biliary tract. It is indicated in the medical management of chronic gall-bladder cases with or without stones, provided there is no actual obstruction. It is of value also in functional hepatic insufficiency, in liver poisoning, by drugs or anesthetics, in cirrhosis, and in chronic passive congestion of the liver. It is *contra-indicated* in *obstructive* jaundice.

Supplied in 3¾ grain tablets—bottles of 50, 100, 500. Dosage 1 to 3 tablets t.i.d. with meals. Literature on request.

ARMOUR *Dehydrocholic Acid*

Have confidence in the preparation you prescribe—specify "ARMOUR"

THE *Armour* LABORATORIES

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

44

Uses for Nembutal

As the published reports pile up—now in the hundreds—short-acting Nembutal is being applied in an increasing variety of conditions. The list at right is only partial. • Because doses adjusted to the need can achieve any desired degree of cerebral depression, from mild sedation to deep hypnosis, short-acting Nembutal naturally lends itself to extensive application. • Small dosage—only about *one-half* that required by many other barbiturates—adds the advantages of shorter effect, reduced possibility of after-effect, marked clinical safety and definite economy to the patient. • In most cases, doses as small as these will suffice: *for mild sedation*, ¼ to ¾ gr.; *for simple insomnia*, ½ to 1 gr.; *for true hypnosis*, 1½ grs.; *for pre-operative medication*, 1½ grs. the night before and 1½ to 3 grs. two hours preceding the operation. • Your pharmacy can supply you with any of 11 Nembutal products in convenient small dosage forms to fit any short-acting sedative and hypnotic need.

In equal oral doses, no other barbiturate combines QUICKER, BRIEFER, MORE PROFOUND EFFECT than . . .

Nembutal®

(Pentobarbital Sodium, Abbott)

ABBOTT LABORATORIES, North Chicago, Illinois.

Sedative

Cardiovascular

Hypertension[1] Decompensation
Coronary Disease[1]
Angina[1]
Peripheral Vascular Disease

Endocrine Disturbances

Hyperthyroid
Menopause—female, male

Nausea and Vomiting

Functional or Organic Disease (acute gastro-intestinal and emotional)
X-Ray Sickness Pregnancy
Motion Sickness

Gastro-Intestinal Disorders

Cardiospasm[2] Pylorospasm[2]
Spasm of Biliary Tract[2] Colitis[2]
Spasm of Colon[2] Peptic Ulcer[2]
Biliary Dyskinesia

Allergic Disorders

Irritability
To Combat Stimulation of Ephedrine alone, etc. [3, 1]

Irritability Associated With Infections[4]

Restlessness and Irritability With Pain[5, 4]

Central Nervous System

Paralysis Agitans Chorea
Hysteria Delirium Tremens
Mania

Anticonvulsant

Status Epilepticus Tetanus
Traumatic Eclampsia
Strychnine Anesthesia

Hypnotic

Induction of Sleep

Obstetrical

Nausea and Vomiting
Eclampsia
Amnesia and Analgesia[6]

Surgical

Pre-operative Sedation
Basal Anesthesia
Post-operative Sedation

Pediatric

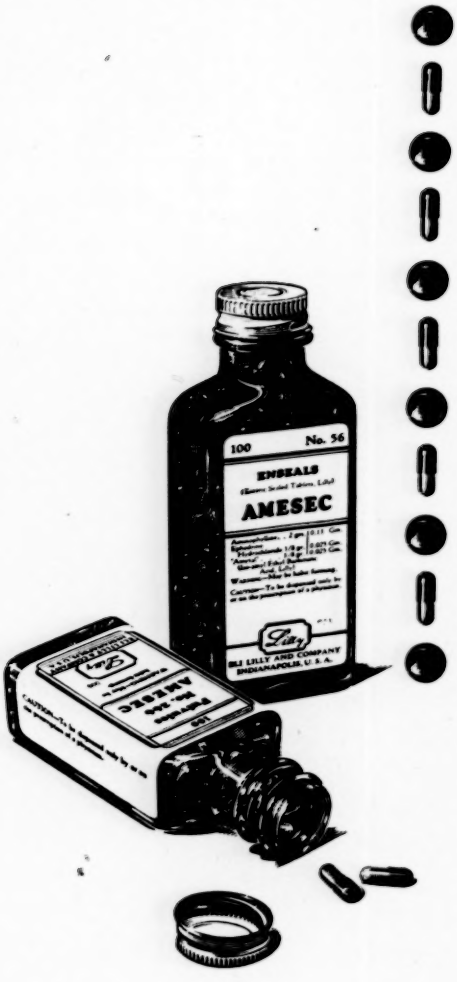
Sedation for:

Special Examinations
Blood Transfusions
Administration of Parenteral Fluids
Reactions to Immunization
Procedures
Minor Surgery

Pre-operative Sedation

Nembutal alone or [1]Glucophylline® and Nembutal, [2]Nembutal and Belladonna, [3]Ephedrine and Nembutal, [4]Nembudeine® [5]Nembutal and Aspirin, [6]administered with scopolamine or other drugs.

continuous symptomatic relief in allergic disorders



● Relief from allergic symptoms usually follows within twenty to thirty minutes after the oral administration of Pulvules Amesec and persists for several hours. Nocturnal attacks may be avoided or mitigated by taking advantage of the timed-disintegration feature of 'Enseals' (Enteric-Sealed Tablets, Lilly) Amesec. One pulvule and one of the 'Enseals' Amesec are taken at bedtime. The pulvule disintegrates promptly and controls symptoms for the ensuing three or four hours. 'Enseals' are timed to disintegrate in from four to seven hours. Thus, the medication is released at approximately the time at which the therapeutic effect of the pulvule is exhausted.

PULVULES AMESEC
. . . for prompt relief of asthma, hay fever, migraine, allergic rhinitis, hypotension, coryza, dysmenorrhea.

ENSEALS AMESEC
. . . for delayed action, to avert nocturnal symptoms.

Formula

Pulvules and 'Enseals' Amesec contain:

Aminophylline	**2 grs.**
Ephedrine Hydrochloride	**3/8 gr.**
'Amytal' (Iso-amyl Ethyl Barbituric Acid, Lilly)	**3/8 gr.**

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The American Journal of Medicine

VOL. III AUGUST, 1947 No. 2

Editorial

A Problem the Physician Must Face

THE past few decades have witnessed considerable progress in the understanding of organic disease. Development and refinement of methods of diagnosis and remarkable strides in chemotherapy have led to more accurate recognition of disease and to a steady decline in the list of fatal disorders. Also during this time almost all organized research in the medical field has been directed toward the solution of problems presented by organic disease. It is, of course, the result of these studies, including the development of new technics in biochemistry, physiology, pharmacology, bacteriology, etc., that such noteworthy progress has been made.

It is natural, therefore, that physicians trained during this period should have had their attention directed primarily toward organic disease. A glance at the current curricula of medical schools shows that this direction of the student's attention has not changed significantly, even today.

The broad increase in knowledge, however, has led inevitably to specialization in practice and this, in turn, has made it more difficult to deal with the patient as a whole. In the days before these advances in medicine, which resulted in the splitting-off of so many specialties, many of the older physicians had the opportunity to know their patients, their families and their activities, and were therefore in a position to appreciate more fully their emotional problems. The same is true of some physicians today but others have failed or refused to recognize these factors even though emotional disturbance is omnipresent. The war brought fresh emphasis upon the frequency and importance of the neuroses and focused attention sharply upon the need of more efficient recognition and therapy for this group.

When young physicians go into the practice of medicine, first during their training period in hospitals and later in their own offices, they find that only four or five of every ten patients have organic lesions related to, or sufficient to account for the patient's symptomatology. The remaining patients, for the most part, present symptoms resulting from emotional problems of varying degrees of severity. When faced with the responsibility for the care of this group, it is only natural that thoughtful physicians should feel that there has been a critical defect in this aspect of their training.

Perhaps many medical schools have already begun to consider means of meeting this problem, but the time is here for all of them, and indeed the whole medical profession, to face the problem squarely. If the majority of patients in the medical practitioner's office are there because of "functional disease" or symptoms produced by emotional disturbances, immediate steps are indicated to equip the practitioner and medical students with methods and technics

that will enable them to handle such problems more intelligently.

This does not mean that organic disease should be neglected or that research directed towards finding its cause and cure should be lessened. Rather, it means that a great deal more attention must be given to the rôle of emotional problems which produce disease and that students must be trained to understand and meet them. Of even greater importance is the fact that a far larger number of capable investigators must be attracted into this field with the hope that new approaches can be made to the study of the problems which are found there. Certainly all will agree that further study is indicated to define more clearly the rôle played by emotional disturbances in the production of disease symptomatology.

Psychiatrists have been developing and employing technics in the treatment of neuroses but it will be the internist, family physician or pediatrician who will be called upon to handle the large majority of mild neuroses and emotional disturbances. The importance of their being able to meet this problem and of knowing when to call for help is obvious. In the more severe neuroses the help of psychiatrists will be needed. The age of specialization has tended to segregate psychiatrists more than any other specialty, but the time has arrived for a much closer cooperation between the internist and the psychiatrist in solving these problems. Both can contribute and both have much to learn, but a freer exchange between the two groups will result in better care for the patient.

JOSEPH T. WEARN, M.D.

Clinical Studies

Intercapillary Glomerulosclerosis*

LOWELL L. HENDERSON, M.D.,† RANDALL G. SPRAUE, M.D.‡ *and* HENRY P. WAGENER, M.D.§

ROCHESTER, MINNESOTA

For years occasional diabetic patients have been observed who presented in varying degrees the clinical picture of albuminuria, nephrotic edema, hypertension, renal insufficiency and retinopathy. In the past such persons have been regarded as diabetic patients suffering from an independent renal or vascular disease which was usually diagnosed as chronic glomerulonephritis, nephrosis or diffuse arteriolar disease with hypertension.

In recent years it has become increasingly apparent that many, though certainly not all, such patients were in reality suffering from a more or less specific degenerative complication of diabetes, differing in certain respects from the common forms of renal and vascular disease observed among nondiabetic persons. This realization had its inception in 1936, when Kimmelstiel and Wilson[12] described lesions of the glomeruli of the kidneys of a group of diabetic patients who during life had presented some or all of the clinical features mentioned in the preceding paragraph. To these lesions Kimmelstiel and Wilson applied the term "intercapillary glomerulosclerosis" because the lesions were characterized by spherical or diffuse hyalin-like masses apparently lying between the capillaries of the glomerular tuft. Since then numerous additional studies[1,2,4,7,10,11,14,19–21] and case reports[3,5,6,8,9,15–18,22] have confirmed in general the original observations of Kimmelstiel and Wilson and have lent support to the idea that intercapillary glomerulosclerosis merits inclusion with retinopathy and neuropathy as a degenerative complication of diabetes. In addition it has become apparent that intercapillary glomerulosclerosis is not always associated with the complete clinical syndrome which was observed in the original cases described by Kimmelstiel and Wilson.

Certain problems related to intercapillary glomerulosclerosis still need clarification. Prominent among them are the questions of the specificity of the lesion for diabetes mellitus, the clinical criteria for its recognition during life, the frequency of its occurrence among diabetic patients, and the relation of the associated changes in the ocular fundi to the lesions in the kidneys. Our purpose in this paper is to present certain observations which have a bearing on these and other relevant points.

MATERIAL AND METHODS

The pathologic material used in this study was as follows: (1) the kidneys of 313 diabetic patients; (2) the kidneys of eighty-one non-diabetic patients on whom a clinical diagnosis of chronic glomerulonephritis had been made; (3) the kidneys of 134 non-diabetic patients whose death had resulted from hypertension and its complica-

* From the Mayo Clinic, Rochester, Minn. Abridgment of thesis submitted by Dr. Henderson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirement for the degree of M. S. in Medicine.

† Fellow in Medicine, Mayo Foundation. ‡ Division of Medicine, Mayo Clinic. § Division of Ophthalmology, Mayo Clinic.

tions; (4) the kidneys, spleen, adrenals, liver and pancreas in twelve cases of amyloidosis; (5) the spleen, adrenals, liver and pancreas in each case from the foregoing groups in which there were advanced lesions of intercapillary glomerulosclerosis; (6) the kidneys of 2,022 routine necropsy cases observed from 1940 to 1943, inclusive, some of them included in the foregoing groups.

In the course of the study a variety of different histologic stains was employed. Specific reference will be made to some of these later.

A clinical study was made of the records of all cases, diabetic and non-diabetic, in which the renal lesions of intercapillary glomerulosclerosis were found. A similar study was made of the records of a group of diabetic patients whose kidneys did not exhibit the lesions, for comparison with the diabetic patients whose kidneys did exhibit the lesions.

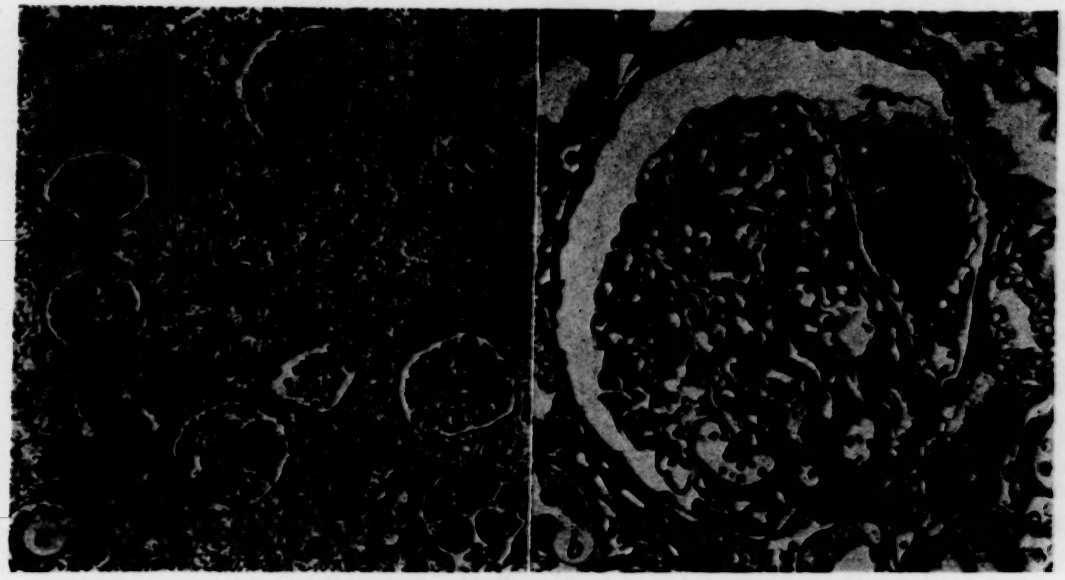
HISTOLOGIC FINDINGS

Types and Incidence of Lesions. It is reasonable to suppose that the lesions of intercapillary glomerulosclerosis pass through a long period of evolution from the time of their inception until they reach an advanced stage. Consequently, the histologic criteria on which to base a diagnosis of intercapillary glomerulosclerosis are not readily defined and the dividing line between kidneys which are said to exhibit the lesions and those which are said not to exhibit them must of necessity be arbitrary. The varying criteria employed probably account for the wide variation in incidence of the lesions (from approximately 20 per cent[4,11] up to 63.7 per cent[14]) in diabetic necropsy material reported by various workers.

Briefly stated, in this study a diagnosis of intercapillary glomerulosclerosis was made if hyalin-like, globular, deeply staining lesions like those originally described by Kimmelstiel and Wilson (Fig. 1), or small deeply staining, club-shaped masses situated in the midst of a diffuse thickening along the axis of the lobule (Fig. 2) could be demonstrated. It was believed that the former type of lesion represented an advanced stage in the development of intercapillary glomerulosclerosis, and that the latter represented an early stage. All other kidneys, including a large group with mild, diffuse thickening, possibly of the intercapillary tissue, were classified as negative for intercapillary glomerulosclerosis. In most instances, the lesions designated as intercapillary glomerulosclerosis were readily identifiable in sections stained with hematoxylin and eosin.

The incidence of intercapillary glomerulosclerosis in 313 cases of diabetes was 19.5 per cent (sixty-one cases). Among the sixty-one cases of intercapillary glomerulosclerosis, the lesions were classified as "early" in thirty-one cases, and "advanced" in thirty cases. Among eighty-one cases of glomerulonephritis affecting non-diabetic patients, the incidence was 12.3 per cent (ten cases). The lesions in seven of the cases in this group were early, and in three they were advanced. Among 134 cases in which the death of non-diabetic patients was due to hypertension and its complications, the incidence was 5.2 per cent (seven cases); in this group there were no advanced lesions.

Association of Renal Arteriolosclerosis with Intercapillary Glomerulosclerosis. All the kidneys, whether from diabetic or non-diabetic patients, in which lesions of intercapillary glomerulosclerosis were found exhibited some arteriolosclerosis. In many instances it was minimal. Not only the afferent and efferent arterioles of the glomerulus were involved, but also the interlobular arterioles. In cases of glomerulonephritis the sclerosis often had the appearance of obliterative endarteritis, apparently due to previous destruction of the glomeruli. In cases of hypertension



A B

C

FIG. 1A. Kidney of a diabetic patient, containing many advanced lesions of intercapillary glomerulosclerosis (× 55); B, glomerulus from kidney of a diabetic patient. There is a large lesion in the center of a lobule, surrounded by a ring of patent capillaries, and many other smaller lesions throughout the glomerulus (× 275); C, glomerulus from kidney of a diabetic patient, containing several advanced lesions. There is considerable sclerosis of the afferent arteriole (× 260).

there were often thickened arteriolar walls typical of malignant hypertension. In the kidneys from diabetic patients there was usually a patchy thickening of the arteriolar walls with considerable hyalinization. While there was at least a rough parallelism between the degree of arteriolosclerosis and the severity of the glomerular lesions in most cases, some glomerular lesions were observed without significant degrees of associated arteriolosclerosis. It, therefore, seems unlikely that arteriolosclerosis is the sole

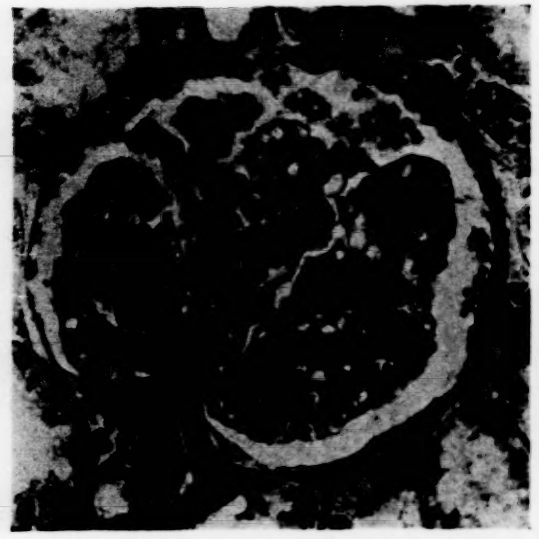


FIG. 2. Glomerulus from kidney of a diabetic patient, showing small, deeply staining, club-shaped masses, classified as early intercapillary glomerulosclerosis (× 300).

etiologic factor in the production of intercapillary glomerulosclerosis.

Differentiation of Intercapillary Glomerulosclerosis from the Glomerular Lesions of Chronic Glomerulonephritis and Amyloidosis. The resemblance between the glomerular lesions in intercapillary glomerulosclerosis, chronic glomerulonephritis and amyloidosis is due to the fact that in each of them, large portions of the glomerulus may consist of a substance which stains homogeneously. As a rule it was not difficult to distinguish between intercapillary glomerulosclerosis and the usual lesions of chronic glomerulonephritis. In the latter disease the sclerosing, hyalinizing process caused a rather marked, diffuse involvement throughout a glomerulus or a large portion of it. Sharply defined spherical lesions like those of intercapillary glomerulosclerosis were not commonly seen. If a single homogeneous mass of material was found, it usually involved at least an entire lobule, and no patent capillaries remained. Also, the relatively mild alterations of renal architecture in most cases of intercapillary glomerulosclerosis contrasted strikingly with the widespread destruction and distortion of the normal structures of the kidneys in cases of chronic glomerulonephritis. In the latter condition many glomeruli were completely hyalinized, and throughout the sections atrophic and degenerating tubules were seen.

There were, however, ten cases of glomerulonephritis, previously diagnosed as such both clinically and at necropsy, in which lesions were found which were indistinguishable from those of intercapillary glomerulosclerosis. In only three of these were the lesions typical of advanced intercapillary glomerulosclerosis. (Fig. 3.) They had the same shape, staining characteristics and general appearance as those observed in the kidneys of diabetic patients. The lesions occurred with too much regularity throughout all the sections studied to be regarded as ordinary lesions of chronic glomerulonephritis which by chance had assumed the appearance of lesions of intercapillary glomerulosclerosis. This evidence suggests that the process which gives rise to intercapillary glomerulosclerosis may occur in the absence of clinically recognizable diabetes.*

Sections of the kidneys from twelve cases of amyloidosis, in six of which there was marked involvement of the glomeruli (Fig. 4), were compared with sections of kidneys from four cases of diabetes in which there were advanced lesions of intercapillary glomerulosclerosis. A variety of histologic stains, including stains for amyloid, was employed. There was not sufficient difference in the staining reactions of the glomerular lesions in the two conditions to permit positive differentiation. Sections stained with Gomori silver showed a greater lamination of the glomerular lesions of intercapil-

* It is of considerable interest, and possibly of some significance, that there was a family history of diabetes in two of the three cases in which a clinical diagnosis of chronic glomerulonephritis had been made but in which the kidneys exhibited lesions typical of advanced intercapillary glomerulosclerosis.

FIG. 3. Glomeruli from kidney of a non-diabetic patient. The clinical diagnosis in this case was chronic glomerulonephritis. The hyaline masses, surrounded by patent capillaries, have virtually the same appearance and staining reactions as the lesions of intercapillary glomerulosclerosis observed in diabetes (× 200).

FIG. 4. Kidney of a non-diabetic patient who had amyloidosis. In the glomeruli are several masses which, seen alone, might be mistaken for intercapillary glomerulosclerosis (× 285).

lary glomerulosclerosis than of amyloidosis, but reliable differentiation on this basis alone was not possible. More positive differentiation was possible when other tissues were studied. In amyloidosis either the spleen or the adrenals or both were involved as severely as the kidneys, while this was not true in intercapillary glomerulosclerosis.

On the basis of the foregoing indirect evidence it seems unlikely that the substance of the lesions of intercapillary glomerulosclerosis is the ordinary variety of what is called amyloid. On the other hand, the fact that, when only the kidneys were considered, it was difficult to distinguish intercapillary glomerulosclerosis from amyloidosis makes one suspect that the degenerative material may be an amyloid-like compound.

Association of Intercapillary Glomerulosclerosis and Hyalinization of the Pancreatic Islets. In the three cases of glomerulonephritis in which there were advanced lesions of intercapillary glomerulosclerosis in the kidneys there was no hyalinization of the islets. Among twenty-nine cases of diabetes in which there were advanced lesions of intercapillary glomerulosclerosis, twelve (41 per cent) exhibited varying degrees of hyalinization of the islets. Since this incidence of hyalinization of the islets is no higher than that found by Warren[26] in a large number of necropsies on diabetic patients, it appears that there is no important relation between the pancreatic and the renal lesions. Incidentally, the data suggest that intercapillary glomerulosclerosis, at least as here defined, is not a more reliable criterion than hyalinization of the islets for the postmortem diagnosis of diabetes mellitus. Laipply, Eitzen and Dutra,[14] on the other hand, considered intercapillary glomerulosclerosis to be the most common pathologic finding which is pathognomonic of diabetes.

COMPARISON OF CLINICAL FEATURES OF DIABETES MELLITUS WITH AND WITHOUT INTERCAPILLARY GLOMERULOSCLEROSIS

As previously stated, the lesions of intercapillary glomerulosclerosis probably pass through a long period of development from their beginning until they reach an advanced stage. It seems likely that the clinical manifestations of the condition would depend on its severity and therefore, if the lesions are progressive, on its duration; that is, very early lesions involving only a small portion of each glomerulus would not disturb renal function, while advanced lesions might be expected to produce the complete clinical syndrome originally described by Kimmelstiel and Wilson, including albuminuria, nephrotic edema, hypertension, renal impairment and changes in the ocular fundi.

Furthermore, if intercapillary glomerulosclerosis is in truth a lesion which occurs for the most part in diabetic persons, it must represent a different pathologic process from those which give rise to the usual forms of renal disease among non-diabetic persons. It might, therefore, be expected that its clinical manifestations would differ in some respects from those of the common chronic forms of renal disease observed among non-diabetic persons.

The analysis of clinical and pathologic data from cases of diabetes, chronic glomerulonephritis, and diffuse arteriolar disease with hypertension suggests that the foregoing lines of reasoning have some foundation in fact. In the material which follows an effort is made to compare the clinical picture of diabetes without intercapillary glomerulosclerosis with that of diabetes with this renal lesion, and later to point out differences between the latter group and non-diabetic patients who were found to have the lesions of intercapillary glomerulosclerosis in association with chronic glomerulonephritis or diffuse arteriolar disease with hypertension.

Age and Sex. Lesions of intercapillary glomerulosclerosis were found among diabetic patients ranging from eighteen to seventy-eight years of age. The lesions occurred with the greatest frequency in the more advanced age groups, the average age being sixty years. The average age of diabetic patients without lesions was about the same (fifty-nine years). In the 313 cases of diabetes studied pathologically, 206 patients were men and 107 were women. The incidence of intercapillary glomerulosclerosis was almost twice as great among the women (twenty-nine instances, or 27.1 per cent) as among the men (thirty-two instances, or 15.5 per cent).

Duration, Severity and Control of Diabetes. The data support the hypothesis that both the occurrence and the severity of the lesions bear a direct relationship to the known duration of the diabetes. In the cases in which advanced lesions were present, the average known duration of diabetes was 11.2 years; in those cases with mild lesions it was 8.1 years, while in the cases without lesions it was 5.2 years. It is probably significant that, among those cases in which the known duration of diabetes was short, but lesions were nonetheless present, the diabetes was always mild and might, therefore, have been present without symptoms for years before it became clinically apparent.

Inasmuch as the average age of the patients exhibiting lesions was sixty years, it would be anticipated that the majority of the patients would have had diabetes of relatively mild degree. This proved to be the case. The average severity of the diabetes was between grade 2 and grade 3, using a system of grading in which 1 is the mildest degree of diabetes and 4 is the most severe.* The average severity in the group

* The system of grading is an arbitrary one employed by the Section on Metabolism Therapy of the Mayo Clinic. *Grade 1* is the designation applied to those cases of mild diabetes in which glycosuria is controlled simply by omitting concentrated sweets from the diet. *Grade 2*

of cases without lesions was the same as that in the group with lesions, suggesting that there is no correlation between the severity of the diabetes and the presence of intercapillary glomerulosclerosis.

Control of diabetes is difficult to estimate in any given case, especially since it is likely to vary from time to time. The impression was gained from a review of the histories of patients with and without intercapillary glomerulosclerosis that there was little difference in the degree of control of the disease in the two groups.

Hypertension. Using a systolic blood pressure of more than 150 mm. of mercury as an arbitrary criterion of hypertension, it was found that 60 per cent of the diabetic patients with intercapillary glomerulosclerosis were hypertensive, as compared to 32 per cent of the diabetic patients without intercapillary glomerulosclerosis. The incidence of hypertension in both groups was 40 per cent, which is in close agreement with the incidence of 39 per cent mentioned by Kramer.[13] It is apparent that hypertension is not an essential part of the clinical syndrome associated with intercapillary glomerulosclerosis.

Cardiac Decompensation. Some writers[16,17] have called attention to a relatively high incidence of cardiac decompensation among diabetic patients suffering from intercapillary glomerulosclerosis. Our data show the same trend. The incidence of cardiac decompensation among the diabetic patients with intercapillary glomerulosclerosis was 33 per cent, as compared to 11 per cent in those without intercapillary glomerulosclerosis.

Edema. This occurred to some degree in 47 per cent of the patients with intercapillary glomerulosclerosis, and in 19 per cent of those without it. In many of the cases of intercapillary glomerulosclerosis in which edema was present, it was associated with cardiac decompensation. In only four of twenty-nine cases of intercapillary glomerulosclerosis in which edema was present could it be classified as the nephrotic type. It is thus evident that edema is not a necessary feature of the syndrome associated with intercapillary glomerulosclerosis, and that when edema does occur it is not always of the nephrotic type.

Association of Intercapillary Glomerulosclerosis with Other "Degenerative" Complications of Diabetes. If intercapillary glomerulosclerosis is in truth a more or less specific complication of diabetes, it should be fairly frequently associated with other complications which are known to be related to diabetes. The following data relative to its association with arteriosclerosis obliterans and gangrene, diabetic neuropathy and diabetic retinopathy tend to substantiate this hypothesis.

(1) Arteriosclerosis obliterans and gangrene:—Arteriosclerosis obliterans and gangrene were found to occur far more frequently among diabetic patients with intercapillary glomerulosclerosis than among those without it. Among the cases with lesions in the kidneys, decrease in the strength of pulsations of the arteries of the feet was recorded in 51 per cent, as compared to 22 per cent in the cases without lesions. These figures are not to be regarded as an accurate indication of the actual frequency of occlusive arterial disease, as there was no record of arterial pulsations in some of the cases, but they are probably a valid indication of the relative frequency of this complication in the two groups. Gangrene of the lower extremities occurred in 12 per cent of the patients who had inter-

---

includes those cases of mild diabetes in which glycosuria is controlled by adherence to a quantitative diet containing approximately 150 Gm. of carbohydrate, without the use of insulin. *Grade 3* includes cases of somewhat more severe diabetes in which satisfactory control cannot be maintained by adherence to an adequate diet alone, but in which, in addition, up to 30 units of insulin daily is necessary. *Grade 4* is the term applied to cases in which more than 30 units of insulin is required daily.

capillary glomerulosclerosis and in 4 per cent of those who did not have it.

(2) Diabetic neuropathy:—This complication also occurred more frequently among patients having intercapillary glomerulosclerosis than among those not having it.

TABLE I

ASSOCIATION OF VARIOUS TYPES OF RETINOPATHY WITH INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETIC PATIENTS; COMPARISON WITH FINDINGS IN THREE SERIES OF LIVING DIABETIC PATIENTS

	Necropsy Cases, This Series		Living Diabetic Patients		
	Intercapillary Glomerulosclerosis Present	Intercapillary Glomerulosclerosis Absent	Series 1921[24]	Series 1934[25]	Series 1945[23]
Diabetic retinopathy: hemorrhages only, per cent	9.4	14.0	3.7	5.5	9.9
Diabetic retinopathy: hemorrhages with punctate exudates, per cent	25.0	3.8	0.7	6.3	8.8
Diabetic retinopathy: hemorrhages with punctate and cotton-wool-like exudates, per cent	25.0	1.2	2.6	2.9	4.6
Diabetic retinopathy: venous disease and proliferating retinopathy, per cent	6.3	0	0	1.9	4.1
Hypertensive retinopathy, per cent	3.1	3.8	1.3	1.1	0.7
Total cases with retinopathy, per cent	68.8	22.8	8.3	17.7	30.6*
Number of cases	32	79	300	1,052	1,021

* Includes 2.5 per cent with retinopathy which was thought to be due wholly or in part to "toxic" factors, not separately listed in the table.

The recorded incidence in the two groups was 23 per cent and 5 per cent, respectively.

(3) Diabetic retinopathy:—While retinal changes associated with intercapillary glomerulosclerosis have been mentioned by several writers, references to this aspect of the problem have to date been rather brief. For the most part, the retinopathy which has been described has been of a type predominantly related to hypertension. The data which follow indicate that the retinal lesions observed in association with intercapillary glomerulosclerosis are predominantly diabetic in type.

Wagener, Dry and Wilder[25] pointed out that diabetic retinopathy is a progressive condition in which the characteristic lesions advance through successive stages in the evolution of a common basic disturbance. They observed the following groups of retinal lesions specifically associated with diabetes mellitus: Group 1, hemorrhages only; Group 2, hemorrhages with punctate exudates; Group 3, hemorrhages with punctate and cotton-wool-like exudates; Group 4, venous disease, with any of the foregoing: (1) without proliferation, and (2) with proliferation.

For purposes of study of retinopathy, the records of 111 cases of diabetes in which necropsy was performed between 1937 and 1943 were reviewed because in all of these examination of the ocular fundi had been done shortly before death, and most of the examinations were performed by one of us (H. P. W.). Of the 111 patients, thirty-two had intercapillary glomerulosclerosis and seventy-nine did not. The incidence of retinopathy among the patients who had intercapillary glomerulosclerosis and among

those who did not have it is summarized in Table 1. For purposes of comparison, data on the incidence of retinopathy in a group of living diabetic patients reported by Wagener and Wilder[24] in 1921, another group reported by Wagener, Dry and Wilder[25] in 1934, and a third group reported by Wagener[23] in 1945 are also given. It is to be noted that the highest incidence of retinopathy was among the necropsy cases having intercapillary glomerulosclerosis (68.8 per cent). In this group the incidence of retinopathy was higher among those cases in which advanced lesions were present in the kidneys (86 per cent) than it was among those cases in which early lesions were present (53 per cent). A considerably lower incidence of retinopathy was noted among the necropsy cases in which intercapillary glomerulosclerosis was not present (22.8 per cent).

A surprisingly high incidence of retinopathy was noted among the group of living diabetic patients examined during 1944 and reported by Wagener in 1945. It is cause for alarm that the incidence of retinopathy in Wagener's 1945 group (30.6 per cent) was almost twice that reported by Wagener, Dry and Wilder (17.7 per cent) in 1934 and the latter figure was more than twice that noted in the 1921 series of Wagener and Wilder (8.3 per cent).

In practically all cases of intercapillary glomerulosclerosis in which retinopathy was present there were lesions in the ocular fundi typical of diabetes. Purely hypertensive retinopathy was present in only one of the thirty-two cases, whereas lesions typical of diabetes were present in twenty-one cases. In many of the latter cases there were changes in the fundi attributable to both piabetes and hypertension; namely, the dunctate hemorrhages and waxy exudates characteristic of diabetic retinopathy, and the superficial hemorrhages, cotton-wool patches, arteriolosclerosis and spastic narrowing of the retinal arterioles characteristic of hypertensive retinopathy. In some instances the changes which are characteristic of diabetes were found only after careful examination of the peripheral portion of the retina.

Inasmuch as the same types of retinopathy, with the possible exception of venous disease, occurred among diabetic patients with and without intercapillary glomerulosclerosis, and inasmuch as in some cases of intercapillary glomerulosclerosis retinopathy was not present, it is obvious that no one type is specifically indicative of the presence of intercapillary glomerulosclerosis. It is also evident that the predominant cause of the retinal changes observed in intercapillary glomerulosclerosis is diabetes rather than renal disease or hypertension.

It is of interest that the incidence of association of the more complex types of retinopathy (that is, groups 3 and 4) with intercapillary glomerulosclerosis was high. Thus, all of the diabetic patients who were found during life to have retinopathy of type 4 were later proved at necropsy to have intercapillary glomerulosclerosis. Likewise, retinopathy of type 3 also had a high incidence of association with intercapillary glomerulosclerosis (eight of nine cases). Retinopathy of types 1 and 2 was less frequently associated with intercapillary glomerulosclerosis. It is thus apparent that, the more complex and advanced the retinopathy, the more likely is its association with intercapillary glomerulosclerosis.

In summary, it can be stated that the retinopathy which occurs in association with intercapillary glomerulosclerosis almost always includes changes which are attributable to diabetes; that retinopathy is far more common among diabetic patients who have intercapillary glomerulosclerosis than it is among those who do not have it; and that the more advanced types of diabetic retinop-

athy are more or less regularly associated with intercapillary glomerulosclerosis.

Laboratory Findings. (1) Albuminuria:—This was observed practically universally among the diabetic patients who later were proved at necropsy to have intercapillary glomerulosclerosis. It occurred in all the cases in which severe renal lesions were present, and in 90 per cent of the cases in which early lesions were present, or in 95 per cent of the entire group. Furthermore, there was a positive correlation between the severity of the renal lesions and the degree of albuminuria. Seventy-six per cent of the diabetic patients who did not have intercapillary glomerulosclerosis exhibited albuminuria of some degree, but it was, on the average, of much lower grade than that of the patients who had intercapillary glomerulosclerosis.

(2) Serum proteins:—There were only four determinations of total serum proteins among the cases of intercapillary glomerulosclerosis, the values being 6.7, 6.6, 5.5 and 4.3 Gm. per 100 cc. of serum. These meager data, and the fact that this determination was not made more frequently, suggest that hypoproteinemia of marked degree is probably not a common manifestation of intercapillary glomerulosclerosis.

(3) Renal function:—Among fifty-five cases of intercapillary glomerulosclerosis in which data were available the blood urea was elevated above the maximal normal level of 40 mg. per 100 cc. in thirty-five (64 per cent), as compared to forty-eight (53 per cent) of ninety-one cases in which intercapillary glomerulosclerosis was not present. The latter group may include a considerable number of selected cases in which determinations of the blood urea were made because the clinicians suspected some abnormality for one reason or another. The average severity of the azotemia differed little in the two groups.

The data on specific gravity of the urine are no more clear-cut. In the collection of these data specimens of urine were chosen which contained no more than traces of glucose, because of the effect of greater amounts of this substance on specific gravity. There was no significant difference in the average specific gravity in the cases in which intercapillary glomerulosclerosis was present (1.022) and in those in which it was not present (1.023).

The foregoing data indicate, at least, that impairment of renal function is not a universal accompaniment of intercapillary glomerulosclerosis.

(4) Anemia:—This was not a common finding among the cases of intercapillary glomerulosclerosis. In only two cases was the erythrocyte count as low as 2,800,000 per c. mm. of blood and in the majority of cases the value was 4,000,000 or more per c. mm. The average erythrocyte count in the cases in which there was intercapillary glomerulosclerosis was 4,100,000, as compared to 4,200,000 in the cases in which it was not present. The average values for hemoglobin in the two groups were 12.1 and 13.2 Gm. per 100 cc. of blood, respectively.

Causes of Death. Disease of the cardiovascular system accounted for the death of thirty-two (52.5 per cent) of the sixty-one diabetic patients who were found at necropsy to have intercapillary glomerulosclerosis. The thirty-two deaths included fourteen due to congestive heart failure, ten due to gangrene, five due to cerebral vascular accidents, two due to myocardial infarction and one due to cardiac dilatation. The only other common cause of death in this group was carcinoma (eight cases, 13.1 per cent). In only one case was death thought to be due to renal insufficiency *per se*.

Among the diabetic patients who were found at necropsy not to have intercapillary glomerulosclerosis, disease of the cardiovascular system accounted for 30.1 per cent of the deaths. Carcinoma was a common

cause of death in this group also (28.5 per cent).

CLINICAL FEATURES OF CASES OF CHRONIC GLOMERULONEPHRITIS WITH LESIONS RESEMBLING INTERCAPILLARY GLOMERULOSCLEROSIS

As previously stated, among eighty-one cases in which the disease had been diagnosed clinically as chronic glomerulonephritis, there were three in which the lesions of the glomeruli were indistinguishable morphologically from those of advanced intercapillary glomerulosclerosis, and seven in which the lesions were similar to those of early intercapillary glomerulosclerosis. The clinical behavior of these ten cases is of theoretical interest because of its bearing on the question of the specificity of intercapillary glomerulosclerosis for diabetes. If the clinical course of these patients closely resembled that of the diabetic patients who had intercapillary glomerulosclerosis, it would lend support to the hypothesis that the lesions of the glomeruli in the two groups were identical, and therefore not associated solely with diabetes. On the other hand, if their clinical course were quite different from that of the diabetic patients, it might be surmised that the lesions of the glomeruli in the patients with chronic glomerulonephritis had merely an accidental morphologic resemblance to those of intercapillary glomerulosclerosis, but in view of their different clinical behavior actually represented a different pathologic process.

A study of the clinical records of the eighty-one patients who had chronic glomerulonephritis disclosed no significant difference between the ten who had lesions of the glomeruli resembling intercapillary glomerulosclerosis and the seventy-one who did not have such lesions. A comparison of the records of the ten who had such lesions with those of the diabetic patients who had intercapillary glomerulosclerosis showed that the two groups were superficially similar: many of the patients in both groups had hypertension, albuminuria, edema and retinopathy. There were, however, several important differences. The average age of the diabetic patients was fifty-eight years, while the average age of the patients who had chronic glomerulonephritis was only thirty-two years. In the cases of glomerulonephritis edema was a more prominent feature than in the cases of diabetes. Among the diabetic patients the retinopathy in almost all cases, as already noted, included some features of diabetic retinopathy, while among the patients who had glomerulonephritis the retinopathy was of hypertensive type.

The clinical course of the two groups of cases was quite different. The terminal illness of the patients who had glomerulonephritis was of one to four months' duration, whereas the diabetic patients lived for months to years after the clinical syndrome associated with intercapillary glomerulosclerosis was fully developed. The cause of death of the patients who had glomerulonephritis was almost always renal or cardiac failure, while the causes of death among the diabetic patients, as already noted, were much more varied. These observations suggest that intercapillary glomerulosclerosis associated with diabetes is a much more benign process than glomerulonephritis with renal lesions resembling intercapillary glomerulosclerosis.

The laboratory findings in the two groups also showed significant differences. Among the cases of glomerulonephritis the anemia was more severe, the hemoglobin averaging only 7.2 Gm. per 100 cc. of blood and the erythrocyte count 2,400,000 per c. mm. of blood; the blood urea was much higher, the average value being 298 mg. per 100 cc.; the specific gravity of the urine was significantly lower, the average being 1.013; albuminuria was more intense, and the

total serum protein was probably lower, averaging 4.6 Gm. per 100 cc.

On the basis of clinical evidence, therefore, it seems probable that the lesions of the glomeruli in the ten cases of glomerulonephritis, while having a morphologic resemblance to intercapillary glomerulosclerosis as seen in diabetic patients, probably represented a different pathologic process.

CLINICAL FEATURES OF CASES OF HYPERTENSION WITH RENAL LESIONS RESEMBLING INTERCAPILLARY GLOMERULOSCLEROSIS

No advanced lesions of intercapillary glomerulosclerosis were found among the cases of hypertension. Early lesions were found in seven cases. There was so much variation in clinical and laboratory findings among these cases that comparison with the cases of intercapillary glomerulosclerosis among diabetic patients was difficult. All seven had hypertension, retinopathy, albuminuria and azotemia. In none of them did the retinopathy include changes attributable to diabetes, and in three of them the retinopathy was that of malignant hypertension. The cause of death in all seven cases was renal or cardiac failure.

From these data it is not possible to draw any conclusions about the identity of the glomerular lesions in these cases of hypertension and those in the diabetic patients who had intercapillary glomerulosclerosis.

COMMENT

Incidence. The wide variations in the reported incidence of intercapillary glomerulosclerosis among diabetic patients who have died depend for the most part on different definitions of the lesion. The incidence of 19.5 per cent found in this series is based on a definition of the lesion which probably excludes some cases in which there are mild lesions. The direct correlation between incidence of lesions and duration of diabetes suggests that intercapillary glomerulosclerosis will be a more and more frequent clinical problem as the average duration of diabetes is increased by better therapy and more effective education of the patient in diabetic care. Unfortunately, there is little in the present study or in other studies to suggest that this complication can be prevented in most instances by careful control of diabetes.

The reported incidence of intercapillary glomerulosclerosis among non-diabetic persons also has varied a great deal. Most writers agree, however, that it is relatively low as compared to the incidence among diabetic patients and that the lesions observed in non-diabetic persons are usually mild. Several other reports are in agreement with our observation that after diabetes mellitus the second highest incidence is in cases in which the clinical diagnosis is chronic glomerulonephritis. In our series, the only non-diabetic cases in which there were advanced lesions were cases of chronic glomerulonephritis.

Specificity of the Lesion for Diabetes Mellitus. The fact that lesions of the glomeruli which are indistinguishable morphologically from intercapillary glomerulosclerosis occur in other conditions than diabetes mellitus forces one to the conclusion that the lesion is not a degenerative complication which is specifically related to diabetes. It is noteworthy, however, that the incidence of the lesion in diabetes is much greater than in any other condition,* and that advanced lesions occur rarely except among diabetic patients. Further, it is noteworthy that in chronic glomerulonephritis, the only other condition in which lesions were found more than just occasionally, the clinical manifes-

* The data of Horn and Smetana[11] are not in agreement with this statement. Their figures on incidence of intercapillary glomerulosclerosis are: diabetes mellitus, 22.9 per cent; arteriolar nephrosclerosis without diabetes, 25.4 per cent; glomerulonephritis, 6.9 per cent; arteriolar nephrosclerosis with diabetes, 59.1 per cent.

tations associated with the lesion were more severe than in diabetes, even though the lesions themselves were, on the average, milder. This curious observation suggests the possibility that the presence of lesions resembling intercapillary glomerulosclerosis is a fortuitous circumstance in some cases of glomerulonephritis, and is not traceable to the same pathologic process as in diabetes.

Clinical Criteria for the Recognition of Intercapillary Glomerulosclerosis during Life. At the present time, there are no certain means available for establishing a diagnosis of intercapillary glomerulosclerosis during life. As emphasized by Bell,[4] there are no definite clinical features by which diabetes with intercapillary glomerulosclerosis can positively be distinguished prior to necropsy from diabetes without intercapillary glomerulosclerosis. Diabetes with intercapillary glomerulosclerosis may have many clinical manifestations in common with diabetes without intercapillary glomerulosclerosis. For example, the presence of minor degrees of albuminuria alone in a diabetic patient is not a reliable indication that intercapillary glomerulosclerosis, as here defined, is present. For the most part, however, the mild lesions are the least likely to give rise to clinical features of diagnostic significance. The presence of advanced lesions, on the other hand, can be predicted with considerable certainty in patients who have diabetes mellitus (particularly diabetes of long duration), albuminuria, hypertension, renal insufficiency and a mixed vascular and diabetic type of retinopathy. But even when all of the clinical manifestations of the Kimmelstiel-Wilson syndrome are present, the diagnosis of intercapillary glomerulosclerosis can be established with complete certainty only by microscopic examination of the kidneys.

Changes in the Ocular Fundi. The results of careful ophthalmoscopic examination of thirty-two diabetic patients in this study who were later shown at necropsy to have intercapillary glomerulosclerosis emphasize that retinopathy is a common accompaniment of this renal lesion. When changes in the ocular fundi are present, they almost always include some features attributable to diabetes. The diabetic features may escape detection if the peripheral zone of the retina is not carefully examined. Among patients who have an advanced diabetic or mixed vascular and diabetic retinopathy the chances of its being associated with intercapillary glomerulosclerosis are great.

SUMMARY

Intercapillary glomerulosclerosis, as herein defined, was found in 19.5 per cent of 313 diabetic patients on whom necropsy examinations were performed. That the lesion is not specific for diabetes, at least morphologically, is shown by the fact that it was found in 12.3 per cent of eighty-one cases of chronic glomerulonephritis and in 5.2 per cent of 134 cases in which death was due to hypertension and its complications. Severe lesions were found only in cases of diabetes and glomerulonephritis, and were by far the most frequent in cases of diabetes. There were important differences in the clinical behavior, respectively, of cases of diabetes and those of glomerulonephritis in which intercapillary glomerulosclerosis was present.

The evidence suggests that intercapillary glomerulosclerosis is a slowly progressive process, related to the duration of the diabetes.

The diagnosis of intercapillary glomerulosclerosis cannot be established with complete certainty during life but the condition can be strongly suspected in patients who have diabetes mellitus of long standing associated with albuminuria, hypertension, renal insufficiency and mixed vascular and diabetic retinopathy. In rare instances the

condition is associated only with diabetes and albuminuria.

Retinopathy is a common accompaniment of intercapillary glomerulosclerosis. In practically all instances it includes features of diabetic retinopathy. The predominant etiologic factor in the retinopathy observed in these cases is usually not the renal disease nor the hypertension, but the diabetes. There are no retinal findings which are specifically indicative of the presence of intercapillary glomerulosclerosis; however, the more advanced types of diabetic retinopathy are more or less regularly associated with this renal lesion.

REFERENCES

1. Allen, A. C. So-called intercapillary glomerulosclerosis—a lesion associated with diabetes mellitus; morphogenesis and significance. *Arch. Path.*, 32: 33–51, 1941.
2. Anson, L. J. Intercapillary glomerulosclerosis. *South. M. J.*, 31: 1272–1275, 1938.
3. Auroi, Marc. Das nephrotisch-hypertonische Syndrom bei Diabetes und die interkapilläre Glomerulosklerose von Kimmelstiel und Wilson. *Schweiz. med. Wchnschr.*, 73: 989–995, 1943.
4. Bell, E. T. Renal lesions in diabetes mellitus. (Abstr.) *Am. J. Path.*, 18: 744–745, 1942.
5. Clarke, B. E. Intercapillary glomerular sclerosis; diabetes-nephrosis syndrome. *Rhode Island M. J.*, 24: 190–192, 1941.
6. Derow, H. A., Altschule, M. D. and Schlesinger, M. J. The syndrome of diabetes mellitus, hypertension and nephrosis. *New England J. Med.*, 221: 1012–1015, 1939.
7. Goodof, I. I. Intercapillary glomerulosclerosis. *Ann. Int. Med.*, 22: 373–381, 1945.
8. Günther, W. H. Intercapilläre Glomerulussklerose bei Diabetes mellitus. *Virchows Arch. f. path. Anat.*, 307: 380–386, 1941.
9. Harrison, T. R. Case report, clinico-pathological conference, Bowman Gray School of Medicine, Wake Forest College. *North Carolina M. J.*, 4: 181–183, 1943.
10. Herbut, P. A. Intercapillary glomerulosclerosis. *Arch. Path.*, 31: 501–507, 1941.
11. Horn, R. C. and Smetana, Hans. Intercapillary glomerulosclerosis. *Am. J. Path.*, 18: 93–99, 1942.
12. Kimmelstiel, P. and Wilson, C. Intercapillary lesions in glomeruli of kidney. *Am. J. Path.*, 12: 83–98, 1936.
13. Kramer, D. W. Hypertension and diabetes. *Am. J. M. Sc.*, 176: 23–31, 1928.
14. Laipply, T. C., Eitzen, O. and Dutra, F. R. Intercapillary glomerulosclerosis. *Arch. Int. Med.*, 74: 354–364, 1944.
15. Mauser, C. L., Rowe, A. H. and Michael, P. P. E. Intercapillary glomerulosclerosis. *Ann. Int. Med.*, 17: 101–105, 1942.
16. Morales, F. H. and Rivera, R. S. D. Intercapillary glomerulosclerosis in Puerto Rico; report of six cases, one with autopsy findings. *Puerto Rico J. Pub. Health & Trop. Med.*, 17: 356–373, 1942.
17. Newburger, R. A. and Peters, J. P. Intercapillary glomerulosclerosis; a syndrome of diabetes, hypertension and albuminuria. *Arch. Int. Med.*, 64: 1252–1264, 1939.
18. Newman, Benjamin. Intercapillary glomerulosclerosis; a syndrome of diabetes, hypertension and albuminuria. *M. Bull. Vet. Admin.*, 21: 86–88, 1944.
19. Porter, W. B. and Walker, Harry. The clinical syndrome associated with intercapillary glomerulosclerosis. *J. A. M. A.*, 116: 459–464, 1941.
20. Siegal, Sheppard. The nephrotic syndrome in diabetes. *J. Mt. Sinai Hosp.*, 6: 264–270, 1940.
21. Siegal, Sheppard and Allen, A. C. Intercapillary glomerulosclerosis (Kimmelstiel-Wilson) and the nephrotic syndrome in diabetes mellitus. *Am. J. M. Sc.*, 201: 516–528, 1941.
22. Simon, M. A. Nephrotic syndrome with hypertension in diabetes mellitus. *Canad. M. A. J.*, 43: 425–430, 1940.
23. Wagener, H. P. Retinopathy in diabetes mellitus. *Proc. Am. Diabetes A.*, 5: 203–216, 1945.
24. Wagener, H. P. and Wilder, R. M. The retinitis of diabetes mellitus; preliminary report. *J. A. M. A.*, 76: 515–517, 1921.
25. Wagener, H. P., Dry, T. J. and Wilder, R. M. Retinitis in diabetes. *New England J. Med.*, 211: 1131–1137, 1934.
26. Warren, Shields. The Pathology of Diabetes Mellitus. 2nd ed., pp. 31–40, Philadelphia, 1938. Lea & Febiger.

Diabetes and Hypertension

EUGENE FOLDES, M.D.
NEW YORK, NEW YORK

WHEN discussing the relationship of diabetes and arterial hypertension, the majority of authors believe that hypertension is more frequent in diabetics than in non-diabetics, the inference being that the metabolic changes of diabetes are favorable to the development of increased blood pressure. As to the effect of hypertension on diabetes, many investigators believe that circulatory changes associated with hypertension predispose to the development of diabetes through circulatory disturbances in the pancreas. Little or nothing is known of the effect of fluctuations in the severity of the diabetic condition upon the level of the blood pressure. In the following this relationship will be considered in connection with a number of cases I had occasion to observe. For the sake of simplicity and convenience, the amount of blood sugar will be taken as an indicator of the severity of the diabetic condition. In some of the cases which will be described, diabetes developed during an observation necessitated by another ailment. In others, the effect of fluctuations of the blood sugar level occurring during diabetic therapy was observed on the blood pressure. In all cases associated with hypertension a relationship between blood sugar and blood pressure was found which, in general, was inverse. In cases in which hypertension was absent there was apparently no relationship between blood pressure and blood sugar during the development of diabetes or following therapy.

CASE REPORTS

CASE 1. Mrs. I. S., age thirty-four, came under observation on October 2, 1930. She complained of irritability and restlessness. Two weeks previously high blood pressure was found by another physician. She had had mumps in childhood. Eight years ago an "ovarian tumor" had been removed. On examination nothing noteworthy was found except a blood pressure of 170/110 mm. Hg. Urine examination, blood chemistry, eyegrounds, etc., were normal.

Subsequent observations, which extended from October 2, 1930, until June 8, 1942, are summarized in Table 1 and Figure 1. It can be seen that following antiretention therapy[1] there was a drop and following the discontinuation of this therapy there was a rise in the blood pressure on several occasions. This relationship is not always clear, possibly either because of characteristics inherent in this case (psychoneurosis, etc.) or because of inaccuracies in the observation of the diet. However this may be, the systolic blood pressure reached 200 mm. or more on occasions and dropped to 150 mm. or less on others. In 1936, diabetes was discovered. Several months prior to the discovery and probably at the time of the onset of diabetes, and presumably at the time of the initial increase of the blood sugar, the blood pressure began to decrease and remained below 160 mm. systolic for over a year with occasional drops to below 130 mm. The blood sugar fluctuated between 210 mg. and 220 mg. at the onset of the diabetes. Under the influence of therapy with diet and insulin it at first ranged between 114 mg. and 183 mg., but during the last two and one-half years of observation it remained constantly below 150 mg. (Following an initial glycosuria there was absence of sugar in the urine.) After the discovery of diabetes, and during the period of the drop in the blood sugar, the blood pressure remained at the previous low level for about six months. Thereafter the blood pressure began to rise, at first to moderate levels and then, year by year, to considerably increased levels. (Table 1 and Fig. 1.)

In this case of essential hypertension the blood pressure dropped simultaneously with the onset of diabetes and returned to the previous high level and beyond following an improvement in the diabetic metabolic state as indicated by the blood sugar.

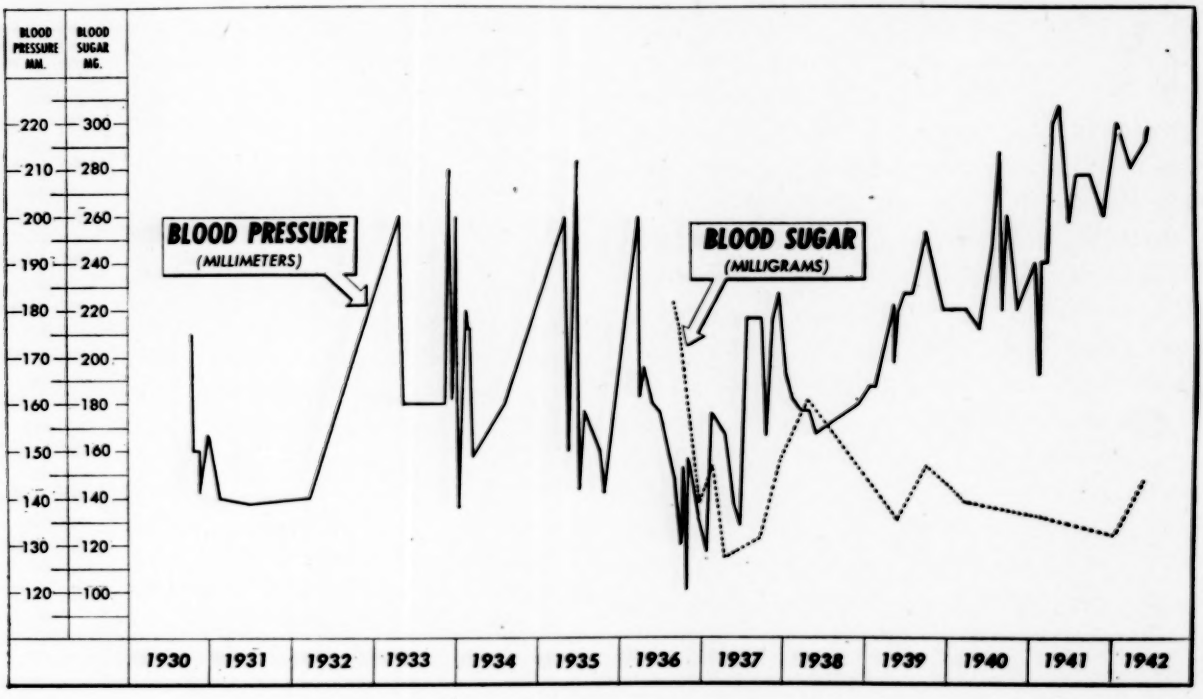


FIG. 1.

CASE II. Mrs. E. D., age sixty, came under observation August 7, 1934. In January, 1934, she had an attack of pain in the precordial region, associated with palpitation. At that time coronary occlusion was diagnosed. Two years prior to and following that attack she had a tight feeling in the chest and palpitation on effort. On examination enlargement of the left ventricle of the heart and impurity of the heart sounds were noted. There was also a mild secondary anemia. The blood pressure was 146/90 mm. The patient has been under observation to date. Mild precordial sensations were present as a rule. Until the end of 1935 the blood pressure readings were normal; they were usually below 130 mm. systolic and 80 mm. or less distolic. (Table II, Fig. 2.) From 1936 there was a slight increase in the blood pressure, 140 mm. or 146 mm. systolic and 80 mm. or 90 mm. diastolic on most occasions. At the end of 1940 there was a further increase, the blood pressure reaching the level of 180/86 mm. (December 19, 1940). From that date on there was a gradual drop in the blood pressure with the exception of March 5, 1942, when a reading of 190/90 mm. was obtained. On March 5, 1942, diabetes was discovered with moderate glycosuria and a blood sugar of 348 mg. A routine urine examination in August, 1941, showed an absence of sugar, so that it may be assumed that manifest diabetes developed between that date and the date of discovery. As in Case I the drop in blood pressure in this case also preceded the discovery of diabetes and, it may be assumed, coincided with the initial increase of the blood sugar. The diabetic condition improved rapidly with the help of diet and insulin, the glycosuria disappeared and the blood sugar dropped to low normal levels, so that the administration of insulin was discontinued on June 15, 1943. (Table II.) Subsequently a moderate increase in the blood pressure developed, the measurements ranging between 138/70 and 162/84 mm.

As in Case I, in this case also the blood pressure dropped simultaneously with the onset of diabetes and gradually increased following improvement in the diabetic met-

TABLE I

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
			4/25/35[1]	200/120		10/6/37	154/94	
10/2/30[1]	170/110		5/8/35	164/100		11/9/37	178/100	
10/6/30	170/110		5/10/35	160/104		12/1/37	184/100	
10/13/30	150/90		5/12/35	150/92		12/4/37		157
10/20/30	150/104		5/14/35	180/114				
11/2/30	150/104		5/16/35	150/86		1/5/38	166/100	
11/17/30	142/96		5/18/35	210/120		2/3/38	162/100	
12/24/30	154/104		5/20/35	164/94		3/24/38	158/100	
			5/22/35	180/110		4/28/38	158/100	183
2/13/31	140/90		5/24/35	212/120		5/25/38	154/100	
6/24/31	138/80		5/29/35	158/94		6/28/38	184/104	
			5/31/35	160/100		11/30/38	160/96	
3/19/32	140/100		6/3/35	142/90				
4/1/32[2]	140/90		6/5/35	164/100		1/16/39	164/96	
			6/8/35	180/110		2/17/39	164/100	
			6/11/35	182/110		5/9/39	182/106	
4/28/33[1]	200/110		6/13/35	152/100		5/11/39	168/100	
5/5/33	160/100		6/15/35	158/96		5/24/39	180/120	131
7/24/33	160/100		9/25/35	150/100		6/24/39	184/100	
11/9/33[2]	160/90		10/19/35[3]	142/100		7/27/39	184/100	
11/27/33[1]	210/120					9/26/39	196/110	156
11/28/33	190/120		3/18/36[1]	200/120		12/7/39	180/100	
12/1/33	184/90		3/25/36	162/94				
12/4/33	168/100		4/6/36	168/100		1/17/40	180/100	144
12/5/33	162/100		5/22/36	160/100		3/26/40	180/100	138
12/8/33[2]	178/100		6/27/36	158/100		5/23/40	176/94	
12/17/33	164/106		8/21/36[3]	145/90	224	7/15/40	194/104	
12/19/33	176/106		8/25/36[4]			8/9/40	214/114	
12/23/33	176/106		9/3/36	144/90		8/29/40	180/92	
12/26/33	200/120		9/9/36	130/84		9/13/40	200/120	
12/27/33	198/104		9/17/36	130/84	214	11/6/40	180/100	
12/30/33	176/104		9/23/36	146/90				
			10/1/36	140/90		1/29/41	190/110	133
1/2/34	168/100		10/8/36	146/90		2/7/41	166/90	
1/4/34	178/100		10/15/36	120/80		2/21/41	190/100	
1/6/34	138/100		10/21/36	148/90		3/12/41	190/100	
1/9/34	176/100		11/6/36	128/70		4/8/41	220/120	
1/11/34	164/88		11/25/36	136/84		5/2/41	224/116	
1/16/34	156/100		12/9/36	134/84		6/19/41	198/110	
1/18/34	148/96		12/24/36	136/74	139	7/23/41	208/108	
1/20/34	154/100					9/12/41	208/100	
1/22/34	180/106		1/21/37	128/80		11/17/41	200/100	
1/26/34	176/106		2/16/37	158/100	154			
1/29/34	176/104		4/16/37	154/80	114	1/6/42	220/120	126
3/6/34	154/100		5/26/37	138/90		3/9/42	210/104	
6/15/34	148/100		6/21/37	134/90		5/27/42	216/110	148
8/2/34	160/100		7/16/37	178/90		6/8/42	218/110	
			9/8/37	178/90	122			

[1] Antiretentional diet begun.
[2] Antiretentional diet discontinued.
[3] Diabetes discovered, urinary sugar 1%.
[4] Diabetic therapy begun with diet and insulin.

abolic state as indicated by the blood sugar.

CASE III. Mrs. T. R., age sixty, began treatment on May 6, 1942. Diabetes had been present for thirteen years. The treatment consisted of diet. Cholecystectomy was performed in 1927. Examination showed a left ventricular hypertrophy of the heart, dilated aorta, blood pressure 170/90 mm, urinary sugar 1 per cent, blood sugar 304 mg. On dietetic therapy glycosuria cleared up but the blood sugar rose to 354 mg. at first. Simultaneously there occurred a drop in the blood pressure to 120/80 mm. When the blood sugar subsequently dropped to between 181 and 192 mg. a gradual rise occurred in the blood pressure to 172/90 mm.

This case showed a rise in the blood sugar which was followed by a drop in the blood pressure. The drop in blood pressure persisted for a while during a period of decreased blood sugar, but then an increase in the blood pressure to the previous level took place.

CASE IV. Mrs. I. P., age seventy-two, began treatment on October 13, 1942. She had had diabetes for twenty years, the treatment consisting of diet and the administration of insulin.

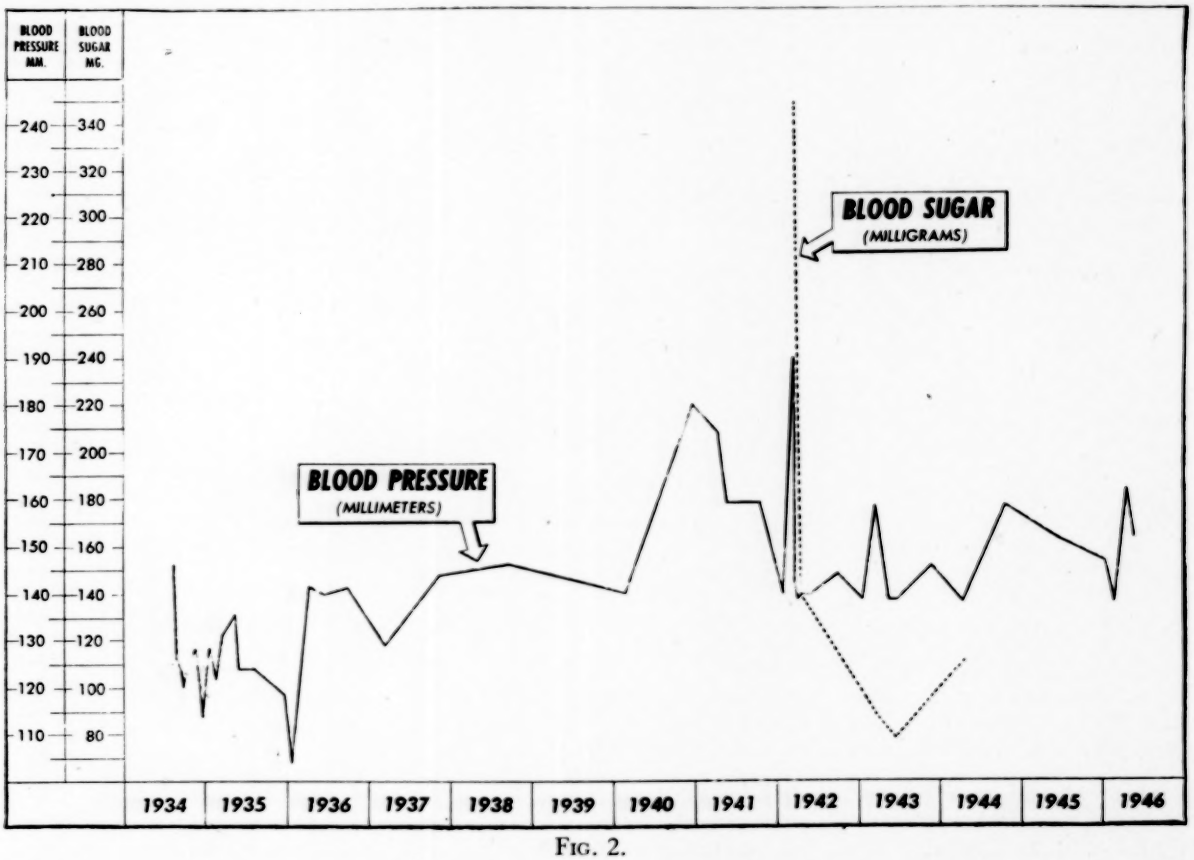


FIG. 2.

Precordial pains on effort and intermittent claudication were present for the last few months. Examination showed the following: hypertrophy of the left ventricle of the heart, left dorsalis pedis artery not palpable. Electrocardiogram: low upright T waves. Urine: 1.2 per cent sugar, blood sugar 217 mg. Following dietetic and insulin therapy there were wide fluctuations in the blood sugar level although urine examination showed absence of sugar, or the presence of traces only. The fluctuations were caused by irregularity in following dietary instructions and by frequent insulin reactions necessitating reductions in the amount of insulin administered. An initial rise in the blood sugar was followed by a considerable drop in the blood

pressure, which drop—similar to the observations in previous cases—persisted for a while in the presence of reduced blood sugar. A further drop in the blood sugar was followed by a rise in the blood pressure, while a subsequent and persistent increase in the blood sugar was associated with a drop in the blood pressure to normal or almost normal levels. (Table IV, Fig. 4.)

TABLE II

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
8/7/34	146/90		4/4/41	174/60	
8/20/34	126/80		5/17/41	158/70	
9/4/34	124/76		8/2/41[1]	158/70	
9/18/34	120/76		10/10/41	158/84	
10/5/34	124/70				
11/2/34	128/74		1/21/42	140/80	
11/23/34	124/76		3/5/42[2]	190/90	348
12/21/34	114/74		3/16/42	142/82	
			3/20/42	138/80	
1/18/35	128/74		4/15/42	140/80	140
2/15/35	122/74		5/28/42	140/70	
3/15/35	132/74		9/18/42	144/86	
5/3/35	126/76				
5/31/35	124/80		1/18/43	138/70	
8/8/35	124/80		3/10/43	158/80	89
11/28/35	118/70		5/13/43	138/70	
			6/15/43[3]	138/76	78
1/17/36	104/70		11/18/43	146/80	
4/3/36	142/90				
6/12/36	140/90		4/4/44	138/70	111
9/25/36	142/80		10/13/44	158/80	
3/5/37	128/80		6/7/45	152/80	
11/5/37	144/80				
			1/8/46	146/80	
9/12/38	146/84		2/15/46	138/70	
			4/9/46	162/84	
2/24/40	140/82		5/7/46	152/80	
12/14/40	180/86				

[1] Urine negative.
[2] Diabetes discovered, urinary sugar 3%, therapy with diet and insulin.
[3] Insulin discontinued.

CASE V. Mrs. L. D., age forty-seven, was first examined on February 27, 1939. Diabetes was discovered two years before, when diet and insulin were administered. She had frequent insulin reactions and difficulty in keeping the urine sugar-free. Physical examination revealed nothing abnormal; blood pressure 130/90 mm., urine contained 1½ per cent sugar, blood sugar 203 mg. The blood sugar, though fluctuating, showed a good response to therapy at first. Later there was a persistent rise caused by frequent insulin reactions which led to reduction of the quantity of insulin administered. The blood pressure was usually normal, or showed a slight increase, indicated by an occasional diastolic pressure of 90 mm. or 96 mm. and a single systolic blood pressure measurement of 156 mm. At best, with such low levels in the blood pressure, no clean-cut relationship can be expected between the blood sugar and a measurement which is so much under the influence of emotional factors as is the blood pressure. However, as shown in Table V and Figure 5, the blood pressure was at its highest in

TABLE III

Date	Blood Pressure, Mm.	Blood Sugar, Mg.
5/6/42	170/90	304
5/15/42	158/80	
5/22/42	140/70	
6/5/42	140/70	
6/26/42	128/80	354
7/17/42	120/80	
8/14/42	138/80	181
9/16/42	120/80	
10/16/42	150/84	190
1/15/43	162/80	192
2/24/43	172/90	

TABLE IV

Date	Blood Pressure, Mm.	Blood Sugar, Mg.
10/13/42	200/100	217
11/6/42	180/80	250
11/13/42	190/90	195
12/4/42	170/80	
12/30/42	158/80	
1/29/43	158/80	147
3/5/43	188/100	
4/12/43	152/70	211
5/18/43	164/90	
6/8/43	166/90	214
7/23/43	166/80	
9/7/43	120/70	231
10/14/43	150/74	

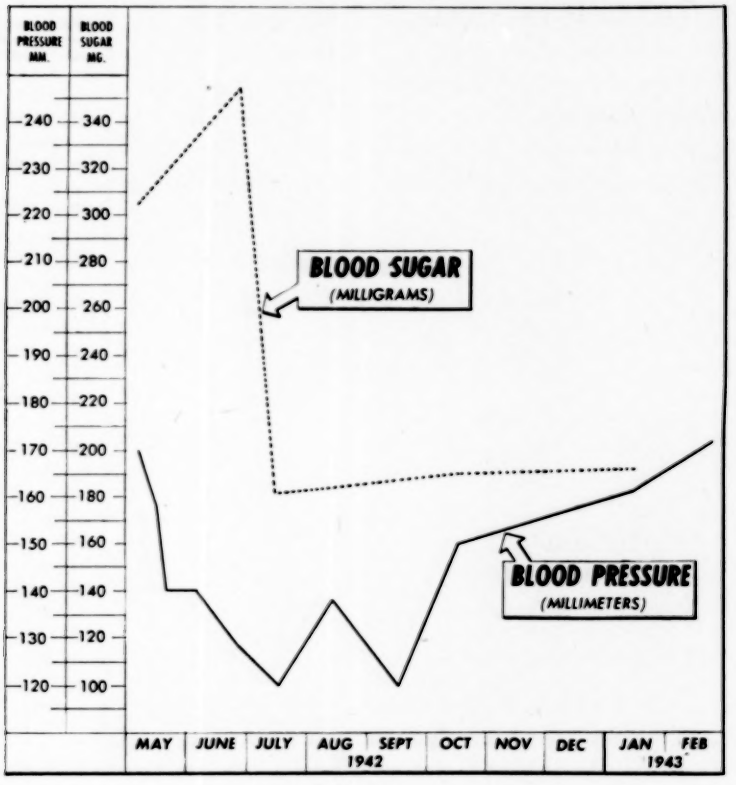

BLOOD PRESSURE MM.
BLOOD SUGAR MG.
240
230
220
210
200
190
180
170
160
150
140
130
120
340
320
300
280
260
240
220
200
180
160
140
120
100
BLOOD SUGAR
(MILLIGRAMS)
BLOOD PRESSURE
(MILLIMETERS)
MAY
JUNE
JULY
AUG
SEPT
OCT
NOV
DEC
JAN
FEB
1942
1943

FIG. 3.

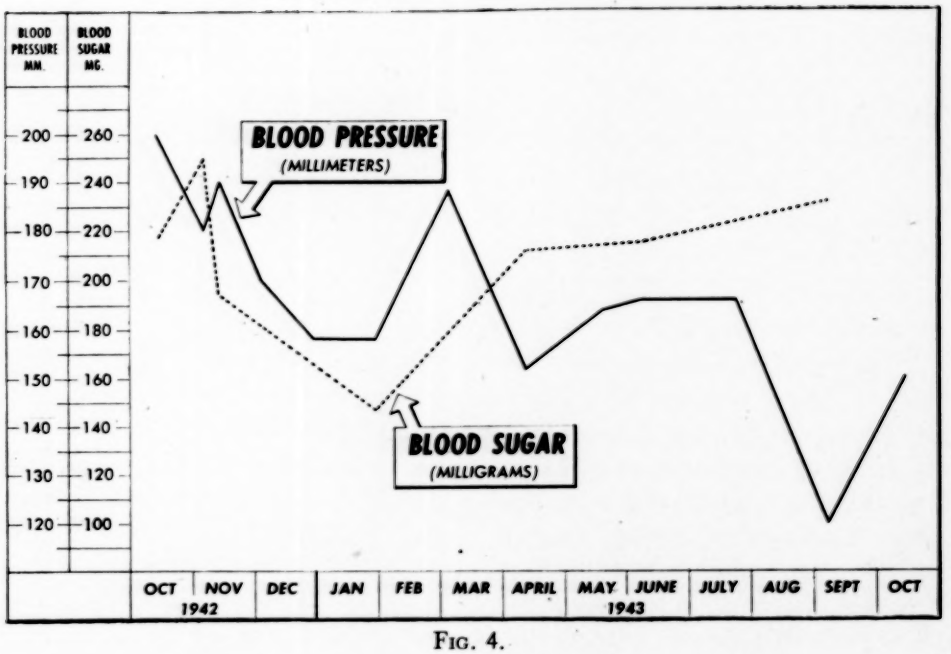

BLOOD PRESSURE MM.
BLOOD SUGAR MG.
200
190
180
170
160
150
140
130
120
260
240
220
200
180
160
140
120
100
BLOOD PRESSURE
(MILLIMETERS)
BLOOD SUGAR
(MILLIGRAMS)
OCT
NOV
DEC
JAN
FEB
MAR
APRIL
MAY
JUNE
JULY
AUG
SEPT
OCT
1942
1943

FIG. 4.

the period in which the blood sugar was at its lowest (June 20, 1939, and September 6, 1939, respectively), and a relatively sudden rise in the blood sugar was followed by a drop in the blood pressure below the "normal" level. (March 18, 1940,—see Table v and Fig. 5.) Also, most

TABLE V

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
2/27/39	130/90	203	4/5/40	128/90	
3/21/39	140/90	164	4/12/40	120/80	
4/1/39	120/80		4/30/40	126/90	
5/5/39	120/70		5/28/40	126/84	
6/20/39		143	8/3/40		220
9/6/39	156/90		9/4/30	128/90	
11/4/39	140/96	164	11/12/40	124/80	188
12/12/39	140/90				
			2/3/41	136/80	
			5/29/41	120/80	316
2/2/40	136/80	188	11/5/41		212
3/18/40	96/68	230			
3/20/40	114/70		3/14/42	132/90	
3/26/40	124/80		4/17/42		318
4/1/40	138/90		6/26/42	140/90	321

frequently, the curve of the blood pressure followed the curve of the blood sugar in reverse, as shown in Figure 5.

In none of these cases was treatment accompanied by considerable gain in weight which might have influenced the blood pressure. In fact, of the five patients four lost weight during the period of observation and the gain in weight of the fifth (Case v) was not more than 2.5 kg. The figures are as follows:

	Body Weight in Kg.				
	Case No. I	Case No. II	Case No. III	Case No. IV	Case No. V
Beginning of observation.....	62	75	73.5	75.5	55.5
End of observation	60	64.5	70	71.5	58

Attention has been called to the fact that development of diabetes is associated with no appreciable changes in the blood pressure in cases in which hypertension is absent. The following example will suffice as an illustration:

CASE VI. Miss W. G., age seventy, was first examined on January 2, 1941. She complained

TABLE VI

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
1/2/41	120/60		5/13/44	124/60	
3/21/41	126/60		5/26/44	140/72	306
4/4/41	130/70		5/31/44	132/70	
5/2/41	126/60		6/6/44	126/60	225
6/3/41	126/62		6/13/44	124/60	
9/22/41	130/70		6/21/44	122/60	86
			6/28/44	114/60	
6/6/42	130/70		9/9/44	110/60	
9/23/42	120/60		9/26/44[2]	120/62	112
			10/24/44	120/64	
9/13/43	128/66		12/1/44	112/56	
1/13/44	124/62		4/11/45	110/50	111
5/5/44[1]	110/60	280	6/12/45	100/50	

[1] Diabetes discovered, urinary sugar 2.8%, insulin therapy.
[2] Insulin discontinued.

of heartburn, belching, poor appetite and constipation. *X*-ray examination showed the presence of gallstones; the other findings were normal. The blood pressure was 120/60 mm. The patient responded satisfactorily to symptomatic treatment. In May, 1944, diabetes was discovered with a urinary sugar of 2.8 per cent and blood sugar of 280 mg. The diabetes was quickly brought under control with the aid of diet and protamin zinc insulin, so that the administration of the latter was discontinued in September, 1944. Even without the administration of insulin the urine of the patient remained sugar-free with a normal blood sugar on an unrestricted diet except for the absence of saccharose. During the entire period of observation to date the blood pressure remained normal (highest systolic blood pressure 140 mm., highest diastolic blood pressure 72 mm.) and no regularity in the relative behavior of blood sugar and blood pressure was found. (Table VI and Fig. 6.)

Similarly, fluctuations in the blood sugar in non-hypertensive diabetics were found not to be associated regularly with fluctuations of the blood pressure.

COMMENT

According to these observations, taking the level of the blood sugar as an indicator of the diabetic metabolic state, development of diabetes or impairment of the diabetic condition in the presence of hypertension, is associated with a decrease in the blood pressure. As a rule, this decrease of the blood pressure persists for a while when improvement of the diabetic condition takes place. Subsequently, if improvement of the diabetes continues, a rise in the blood pressure occurs. In the absence of hypertension no relationship between blood pressure and blood sugar is observed. The presence of such a relationship may exist, but may not be detectable because of the many factors which influence the blood pressure. Some of these factors other than the blood sugar level may be relatively insignificant in the presence of hypertension but sufficient to obscure the picture when the blood pressure is normal.

As to the mechanism of the relationship between blood sugar and blood pressure, I advanced the theory that in the pathogenesis of arterial hypertension increased blood volume, whether existing in itself or as a part of general fluid retention, is a significant factor.[1] Reduction of such fluid retention by antiretentional diet or other means is followed by significant reduction of the blood pressure in many instances.[1] This was later confirmed by a great number of unpublished observations of my own as well as by the observations of others.[3,4,5,6] In diabetes, glucose, if eliminated in consider-

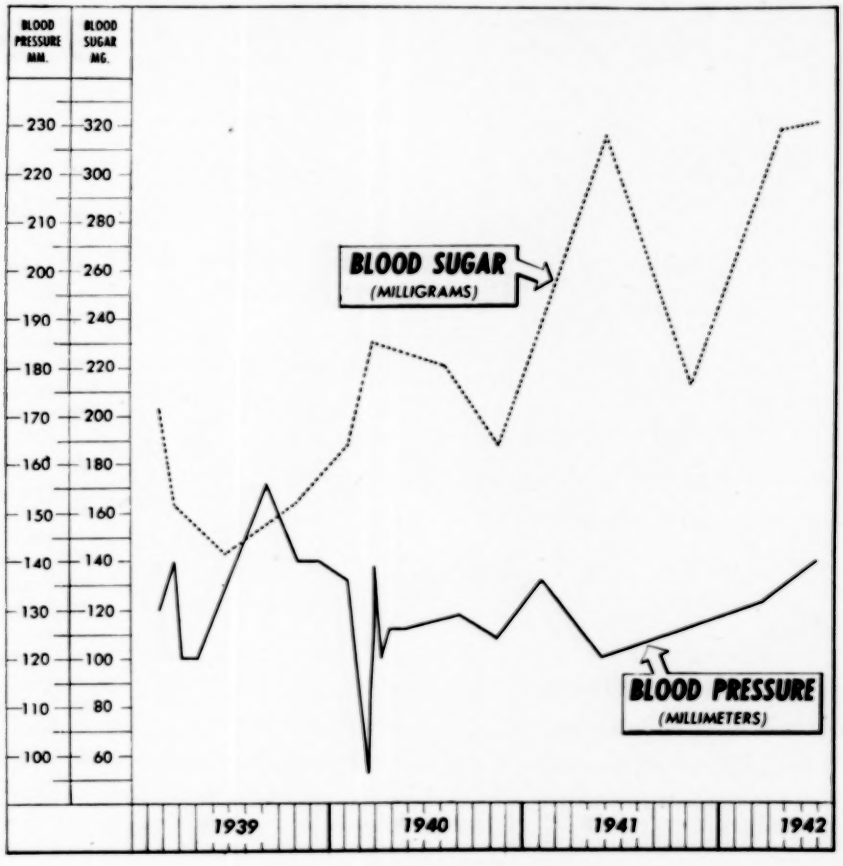


FIG. 5.

able amounts by the kidneys, acts as a powerful diuretic and leads to the well known phenomenon of polyuria (and frequently to dehydration). I had occasion to show how water retention and edema caused by certain factors are counteracted by the diuretic effect of eliminated glucose.[2] The possibility may here be considered that hyperglycemia and associated glycosuria and polyuria act as antiretentional therapy; hence the reduction of the blood pressure level. When the diabetic state improves and hyperglycemia and glycosuria decrease, retention again develops and the hypertension increases. In view of the fact that the decrease in blood pressure usually outlasts the glycosuria and hyperglycemia, it would be necessary here to assume that the dehydrating effect of the glycosuria persists for a period beyond the actual polyuria, and that considerable time is required for further retention to develop in the organism. This would correspond to observations made in cases in which an antiretentional diet was applied in essential hypertension, and in which the reduction in blood pressure frequently persisted for a period after the diet had been discontinued.

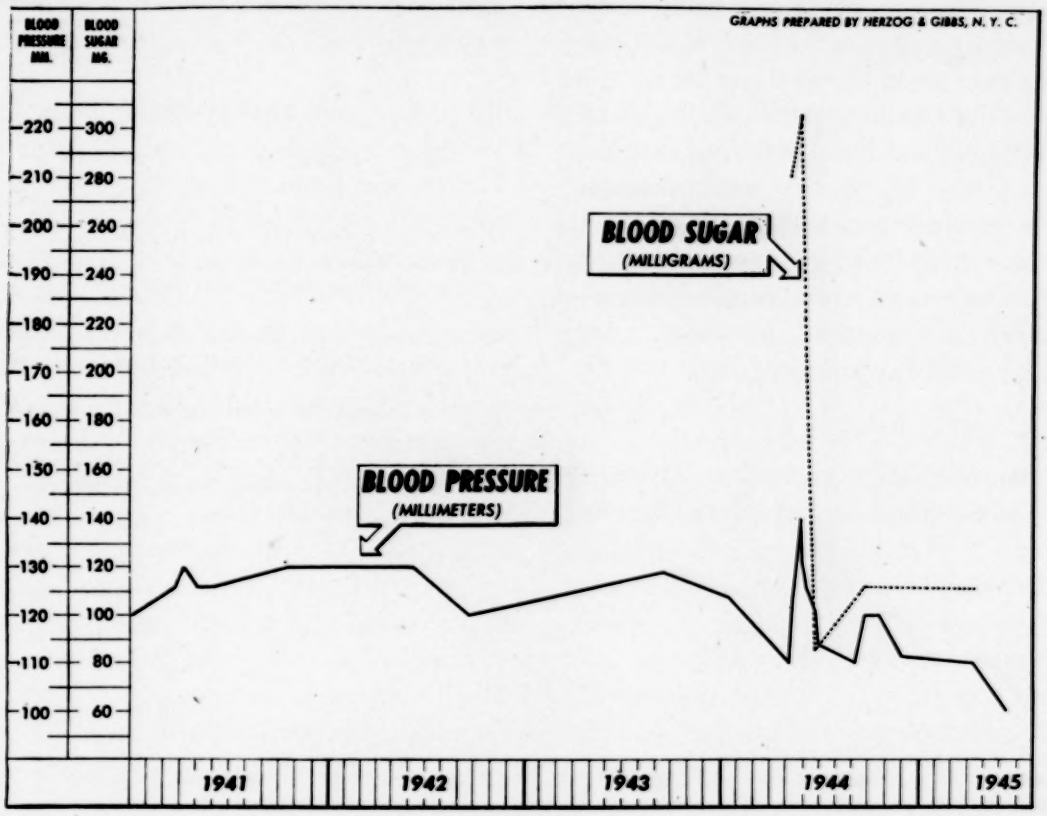


FIG. 6.

Other concepts of the mechanism of the effect of the fluctuations in blood sugar on the blood pressure are also admissible. In particular, involvement of the endocrine glands may be considered. It is possible that a drop in the blood sugar acts as a stimulant to those endocrine glands which influence both the blood sugar and the blood pressure in a positive direction (*vide* for instance the effect of the adrenal cortical hormone on the blood sugar and on the blood pressure). The increased output of a hormone which raises both the blood sugar and the blood pressure would thus lead to increased blood pressure; and conversely, a rise in the blood sugar would decrease stimulation of

such gland or glands, and that would then lead to diminished blood pressure.

It remains for further investigations to show which concept best corresponds to the facts.

As a practical consideration the following should be mentioned. If increased blood sugar leads to a decrease of the blood pressure, and decreased blood sugar leads to an increase of the blood pressure, the usual aim in medical practice of normalizing the blood sugar may not be to the best advantage of the hypertensive diabetic patient. It is conceivable that it might be more advantageous to standardize the blood sugar at a moderately increased level in order to keep the hypertension at a lower level.

SUMMARY

1. Cases of diabetes associated with hypertension are presented in which the effect of fluctuations of the blood sugar level on the blood pressure was observed. In these cases an inverse relationship existed between the level of the blood sugar and that of the blood pressure.

2. No such relationship was found to exist in diabetics in the absence of hypertension.

REFERENCES

1. Foldes, Eugene. A New Approach to Dietetic Therapy. Boston, 1933. R. G. Badger.
2. Foldes, Eugene. Diabetic edema and acidosis. *Wien. Archiv f. inn. Med.*, 3: 469, 1922.
3. Gold, Harry. Conferences on therapy. The use of mercurial diuretics. *New York State J. Med.*, 46: 62, 1946.
4. Goldzieher, M. A. and Salmovitz, S. Endocrine aspects of hypertension. *J. Clin. Endocrinol.*, 3: 37, 1943.
5. Johns Hopkins Hospital Manual of Applied Nutrition. The Johns Hopkins Hospital Diet Dept., 1941.
6. Strauss, M. B. The etiological relationship between water retention and arterial hypertension. *Am. J. M. Sc.*, 196: 188, 1938.

898 *Park Ave.*

Insulin Mixtures

*An Evaluation of Their Use in 150 Cases**

WILLIAM S. COLLENS, M.D., LOUIS C. BOAS, M.D. *and* JAMES D. ZILINSKY, M.D.

BROOKLYN, NEW YORK

SHORTLY after the discovery of insulin it was found that soluble, amorphous insulin was too evanescent in its action and required the daily injection of multiple doses, especially for the satisfactory control of severe diabetics. Insulin has since undergone periodic modifications intended to make it a smoother acting preparation, one which would free the patient from hypoglycemic reactions and eliminate the necessity for multiple injections during the course of the day.

Attempts at retardation of the insulin effect were first made by Leyton.[1] He suspended solutions of insulin and of dry insulin powder in oil and in oil-emulsions. He found that there was no difference in its action. The insulin was rapidly taken up by the blood serum in all cases. The problem then was approached by preparing a precipitated compound of insulin which was sparingly soluble in the body and would thus release the insulin slowly. Gray[2] prepared an insulin tannate which had the property of acting longer than ordinary insulin. Jacobs and Ricketts[3] succeeded in obtaining a prolonged and retarded insulin action by precipitating insulin with safranin. Rosenthal and Kamlet[4] produced a similar effect by precipitating insulin out of solution with alum. Hagedorn et al.[5] precipitated insulin with protamine. Hagedorn selected the monoprotamine from the sperm of Salmo iridens for precipitating insulin, because the precipitate has the lowest solubility of all the protamine insulin compounds. This proved to be the most successful compound thus far prepared.

It soon became apparent that although protamine insulin was smoother acting than unmodified insulin and eliminated the necessity for multiple injections, it possessed certain disadvantages. One of its chief defects was that too long a delay occurred in the production of an insulin effect after injection. A significant insulin effect does not become apparent for a period of six to eight hours after injection. The injection of protamine insulin before breakfast fails to provide a satisfactory insulin effect during the prandial period of the same day but produces the peak of its action in the postprandial period. This imposes a specific disadvantage in the severe diabetic since it becomes necessary to give a dose of protamine insulin large enough to be effective the following day. Such large doses, frequently of 100 to 125 units, have the undesirable property of producing hypoglycemic reactions, especially in the early morning hours. In order to circumvent this disadvantage of protamine zinc insulin, a technic was evolved of providing the patient with a supplementary dose of unmodified insulin as a separate injection at the same time that the protamine insulin was injected. It was found that these two injections had to be administered before breakfast in order to produce the most satisfactory form of control.

* From the Department of Medicine, Israel Zion Hospital and the Metabolic Department, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.

This led to a search for some form of insulin which in its action would hold an intermediary place between soluble unmodified insulin and precipitated protamine zinc insulin. One of the results of this line of investigation was the discovery of a loosely bound compound of globin and insulin.[6] It was observed that in the duration and intensity of its action, globin insulin holds an intermediary position between soluble unmodified insulin and protamine zinc insulin. Although some of the earlier reports on the use of this agent appeared to be very favorable, our own experience revealed to us that globin insulin has a mildly retarded action, incapable of maintaining an insulin effect for twenty-four hours unless given in large doses. This proved to be a disadvantage in the severe diabetic because such patients became susceptible to severe hypoglycemic reactions six to eight hours after the administration of this agent.

An interesting series of investigations has recently been reported describing the results of mixing unmodified insulin with protamine insulin. This technic originated with Graham[7] who found that mixing the insulins gave a preparation which possessed some of the characteristics of both quick-acting unmodified insulin and long-acting protamine insulin. Ulrich[8] later pointed out that if a sufficiently large amount of unmodified insulin is added to protamine insulin a point is reached beyond which unmodified insulin remains intact in the mixture. The first important practical contributions which made mixtures clinically feasible were those of Colwell et al.[9] and Peck.[10] They showed that when soluble insulin is added to protamine insulin in the proportion of two or three parts soluble insulin to one part protamine insulin, intermediate effects are obtained without influencing the prolonged action of protamine insulin.

In December, 1943, we decided to institute the use of insulin mixtures in a series of diabetics under our observation. Since then we have accumulated experience with one hundred fifty patients. Primarily we followed the technics of the previous investigators in this field, but quickly found that employing mixtures of two parts unmodified insulin to one of protamine, or three parts of unmodified insulin to one of protamine, did not achieve the goal of adequately controlling all the diabetics. We found that the use of one or even two fixed ratios was not suitable in all cases. In our series the required range of ratios of mixtures was between one part soluble insulin to one part protamine insulin, and five parts soluble insulin to one part protamine insulin. In no case did we find it necessary to give a ratio of less than 1:1.

Mixtures were prepared by the patients who mixed each dose in the insulin syringe at the time of administration. This was done according to the following directions which were given to the patients:

DIRECTIONS FOR USING
INSULIN-MIXTURE

1. Draw up air to the _____ mark.
2. Inject the air into the regular insulin bottle and withdraw insulin to the _____ mark. Then withdraw needle from insulin bottle.
3. Hold syringe upside down. Draw air into syringe till piston reaches_____ mark.
4. Shake protamine insulin bottle vigorously.
5. Insert needle in the bottle of protamine insulin and inject the *air only* into the bottle. Withdraw protamine insulin to the _____ mark.
6. Draw in air bubble into syringe and mix.
7. Turn syringe upside down and expel bubble.

8. You are now ready to administer the insulin mixture.

No patient was permitted self-administration of insulin mixtures until we were convinced that he had mastered the technic.

RESULTS

We considered a patient satisfactorily transferred to insulin mixtures when glycosuria was minimal, the blood sugar as close to normal as possible and the patient was maintained in a satisfactory nutritional state, felt clinically well and was free from hypoglycemic reactions. The results reported are based upon observations made in 150 cases over a period of two years. Figure 1 presents a graphic summary of all the cases studied, showing the distribution of the ratios of unmodified to protamine insulin employed in the mixtures. It will be seen that fifteen cases were satisfactorily controlled on a mixture of one part soluble insulin to one part protamine insulin; twenty-one patients on 1½ parts soluble insulin to 1 part protamine insulin; seventy-nine patients took a mixture of 2 parts soluble insulin to 1 part protamine insulin; fifteen patients took 2½ parts soluble insulin to 1 part protamine insulin; fourteen took 3:1; and four took 5:1 of soluble insulin to protamine insulin.

It will be seen that only 53 per cent of all cases were satisfactorily maintained with a mixture of 2 parts soluble insulin to 1 part protamine insulin. We attempted to analyze these cases for the purpose of finding some equation or formula by means of which one could predict the proportion of mixtures necessary to maintain each patient. In Figure 2 is seen a breakdown of the cases showing the mixtures employed in patients, compared with their previous management when they received separate injections of soluble insulin and protamine insulin. There does not appear to be any relationship which would help us to predict the requirement of insulin mixtures based upon previous separately injected doses. It still appears that regardless of the ratio of separately injected doses previously administered, the majority of the patients receiving mixtures found it necessary to take a 2 to 1 proportion of soluble insulin to protamine insulin.

The question then arose as to whether there was any relationship between the severity of the disease and the ratio of mixtures necessary to control the diabetes. Figure 3 is a composite curve showing the range of ratios employed in relatively mild diabetics and in severe diabetics. The total insulin requirement of the day was used as an index to the severity of the disease. This was considered permissible since all the patients were given high carbohydrate diets. Those taking less than 40 units per day were arbitrarily classified as relatively mild diabetics, and those taking more than 70 units per day as severe diabetics. It will be seen from Figure 3 that irrespective of the mildness or severity of the disease, the great majority of patients taking mixtures were best controlled with a proportion of 2 parts of soluble insulin to one part protamine insulin. The pattern of the curve is similar to the curve for all cases as seen in Figure 1.

It would thus appear that no factor in the previous management of the patient serves as a reliable index or criterion for predicting the proportion of soluble insulin to protamine insulin to be employed in mixtures.

Besides the statistical analysis of the cases just presented, the following are pertinent observations made regarding the clinical results with patients transferred to mixtures.

In the first place, it was observed that the frequency of hypoglycemic reactions was reduced. It was also observed that a shift in the peak of intensity of insulin activity occurred when the patients were transferred from separately injected doses to insulin mixtures. The sharpness of the action of unmodified insulin when given as a separate

injection supplementary to the protamine insulin in the morning before breakfast generally creates a tendency for reactions to occur (if they do occur) four hours after the injection. With this technic, therefore, reaction consists in the provision of a supplementary intercibal feeding two hours after breakfast, with the patient taking lunch within four hours after taking insulin.

The use of insulin mixtures appears to

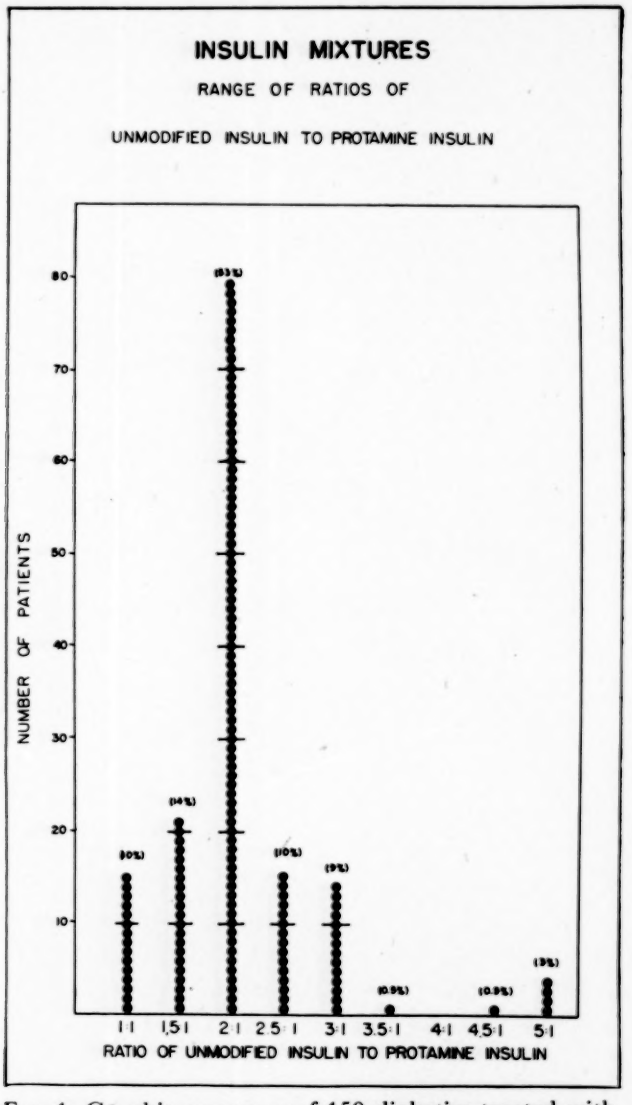


FIG. 1. Graphic summary of 150 diabetics treated with insulin mixtures. Note that 53 per cent of all the patients were successfully treated with a mixture of two parts unmodified to one part protamine insulin. The balance required mixtures ranging between 1:1 and 5:1 of unmodified to protamine insulin.

patients are susceptible to hypoglycemic symptoms before lunch when the insulin is administered in the morning before breakfast. Of course, a satisfactory practical procedure to circumvent the hypoglycemic obviate the sharpness of action of unmodified insulin, and what is left as soluble insulin seems to serve as an intermediate-acting insulin apparently producing a peak of activity six to eight hours after injection.

It was observed that patients who take mixtures are susceptible to reactions six to eight hours after the injection. This means that hypoglycemic symptoms, if they occur, develop in the late afternoon when the patient takes mixtures in the morning before breakfast. In order to circumvent this, it was found necessary to provide a supplementary feeding six hours after the administration of the insulin mixtures.

It was found also that patients prefer the use of mixtures because one injection is eliminated. This appears to be one of the chief advantages in most of the patients previously best maintained with separately injected doses of insulin. Most patients also reported a better sense of general well-being. In the case of one juvenile diabetic, the mother noticed that the behavior of the child appeared more normal. Weight gain has been more consistent, especially in some juvenile diabetics.

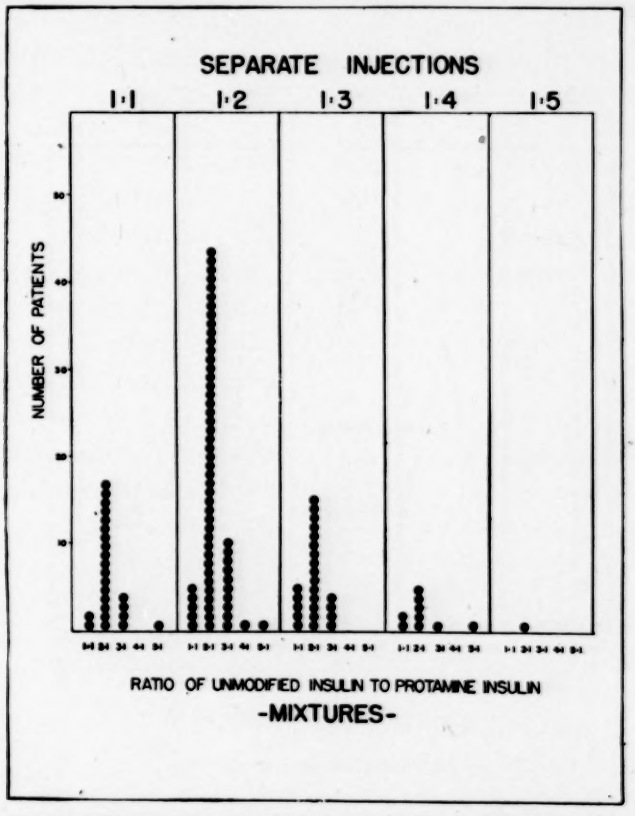


FIG. 2. This graph reveals the ratio of unmodified insulin to protamine insulin required in a mixture for patients who had previously received separately injected doses of unmodified and protamine insulin. It will be seen that regardless of the previous ratios of separately injected doses, the majority of the patients in each group required a ratio of two parts unmodified to one part protamine insulin in the mixture.

In contrast to these apparent advantages, there appeared to be certain disadvantages in the use of insulin mixtures. One of the chief disadvantages of insulin mixtures is that their action is less predictable than that either of unmodified insulin or protamine insulin when given alone or as separately injected doses in the morning be-

fore breakfast. Insulin mixtures appear to be easily inactivated by infection. This becomes quickly apparent in the severe diabetic who experiences an acute upper respiratory tract infection. The patient may be evenly controlled and well stabilized with a specific dose of a mixture but within twenty-four hours of the onset of an infection will show a severe break in carbohydrate tolerance even though he maintains the same regularity of treatment. Another important disadvantage in the use of insulin mixtures is the necessity for closer attention to the details of dietary management by the patient and to follow-up care by the physician. The lack of predictability of the action of mixtures makes necessary meticulous care in timing the feeding after injection of the mixture. Carelessness on the part of the patient in missing the supplementary feeding in the afternoon, or even in being late for the feeding, makes him susceptible to hypoglycemic reactions.

The introduction of insulin mixtures has also added a complicating difficulty to the physician's practice. A patient cannot be managed satisfactorily on insulin mixtures unless adequate information is obtained on the intensity and duration of effect of insulin mixtures in the course of the twenty-four-hour cycle. This requires an analysis of fractionally excreted specimens of urine voided over twenty-four hours, in addition to an examination of the fasting blood sugar. Besides this, the carbohydrate, protein and fat value of all foods taken in each meal and

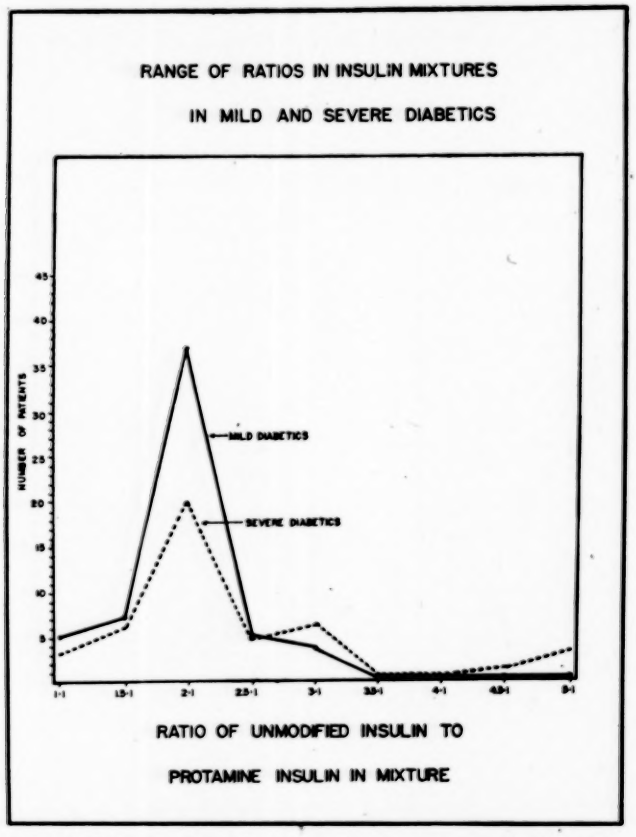


FIG. 3. Range of ratios of insulin mixtures employed in mild and severe cases of diabetes. Note that the curves run almost parallel indicating that the severity of the disease did not predetermine the ratio of the mixture.

the supplementary feedings between meals on the day that the urines are collected should be calculated.

Another important disadvantage in the use of insulin mixtures is that the patient must manufacture his own dose every time he takes his injection. Our experience indicates that any attempt to simplify the use of insulin mixtures by having pre-mixed insulin on the market, prepared by the manufacturer, physician or patient, is not the most satisfactory method of employing mixtures. Although we have found that 53 per cent of our patients are satisfactorily maintained with mixtures averaging 2 parts soluble insulin to 1 part protamine insulin, there still exists the large group of 47 per cent of patients who require mixtures in different ratios ranging from 1:1 to 5:1 of unmodified to protamine insulin. The introduction of pre-mixed insulins in such wide ratios would only tend to confuse a situation already complicated by the varieties of insulin available to the patient.

Although the statistical study in Figure 1 indicates that 53 per cent of the patients are satisfactorily maintained on a 2:1 mixture of soluble to protamine insulin, it must be stated at this point that this is only an average figure. For example, a patient who uses 55 units of unmodified insulin and 30 units of protamine insulin is classified as one taking a 2:1 mixture. Similarly, a patient receiving 70 units of unmodified insulin and 30 units of protamine insulin is also classified as taking a 2:1 mixture. The wide disparity of these two mixtures is easily seen and yet in classifying patients for average computations, the details of such mixtures are lost. A detailed breakdown of our cases indicates that the number of patients receiving an exactly 2:1 mixture represents only 20 per cent of the entire series. This again indicates that satisfactory control of the diabetes can be effected only if the patient prepares each dose.

The follow-up visit furnishes the physician with information which enables him to modify the particular ratio which the patient is receiving. Thus, the character of the prandial glycosuria, as obtained from fractional urine studies, serves as an index for establishing the dose of unmodified insulin in the mixture; while the fasting blood sugar serves as a guide to the dose of protamine insulin in the mixture. It has been our experience that while a patient may be started with a mixture in the exact proportions of 2:1, information gained from the follow-up visit might result in satisfactory control with only slight alteration of the ratio.

CASE REPORTS

CASE I. A. J., male, fifty-two years of age, has been a diabetic for the past four and one-half years. He was treated with a maintenance diet and separately injected doses of unmodified and protamine insulin up to October 6, 1944. From then on he was shifted to insulin mixtures. The diet has remained fairly constant throughout the period of observation, with an average intake of 200 Gm. of carbohydrate, 80 Gm. of protein and 125 Gm. of fat. His weight for two years before mixtures fluctuated between 134 and 144 pounds. After institution of insulin mixtures, his weight increased to an average of 150 pounds. He has experienced no reactions either on separately injected doses or on mixtures. He feels generally better since his weight increased. A graphic summary of his case for one year on separately injected doses and one year on insulin mixtures is seen in Figure 4. It will be observed that the prandial glycosuria appears to be less with insulin mixtures and the fasting blood sugars have been more frequently normal. It will also be observed that the total insulin requirements are approximately the same. The ratio of unmodified to protamine insulin in the mixtures has fluctuated between 1 to 1 and 1:5 to 1.

CASE II. T. M., a nineteen year old male, developed diabetes when he was twelve years of age and has been under our observation since

the onset. His carbohydrate tolerance has been relatively constant during the past five years during which time his total insulin requirements have averaged approximately 60 units per day. His dietary intake has also been relatively constant averaging approximately 275 to 300 Gm. tensity of the glycosuria. His weight has remained constant throughout. He has experienced occasional mild insulin reactions under both regimens. His reactions occurred in the morning before breakfast on separate injections. He experienced occasional reactions in the late

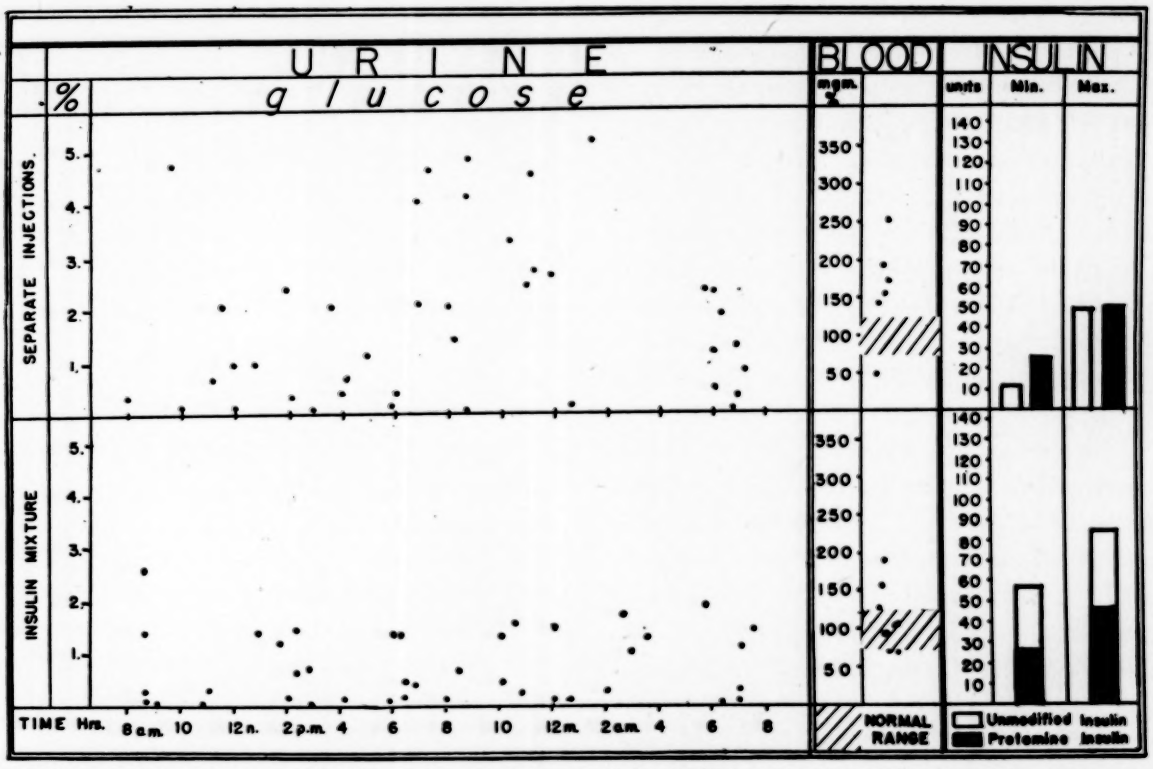


FIG. 4. Graphic summary of a fifty-two year old male diabetic (Case I in the text), comparing one year of treatment with separately injected doses of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the total insulin requirements are approximately the same, the fasting blood sugars are more frequently normal on mixtures and the glycosuria is less intense on mixtures, especially in the afternoon.

of carbohydrate, 100 to 120 Gm. of protein and 100 to 125 Gm. of fat. On April 5, 1944, he was transferred from separate injections of regular insulin and protamine insulin to insulin mixtures. Figure 5 is a graphic summary of this patient's status for one year before and one year after the institution of mixtures. His general physical condition has remained good and there have been no serious complications. His total insulin requirements are approximately the same on both regimens. It will be seen that the fasting blood sugar on treatment with mixtures is closer to the normal range but there has been practically no change in the character or incidence of the glycosuria. His weight has remained constant throughout. He has experienced occasional mild insulin reactions under both regimens. His reactions occurred in the morning before breakfast on separate injections. He experienced occasional reactions in the late afternoon on mixtures. In every case these reactions occurred when the patient was late for his intercibal supplementary feedings. He was best maintained on a mixture of 2 parts regular and 1 part protamine insulin.

CASE III. F. K. is a twenty-one year old female who has been diabetic since she was eleven years of age and has been under our observation since she was sixteen. She is a severe diabetic and has been maintained in a state of well-being on a diet averaging 225 Gm. of carbohydrate, 100 Gm. of protein and 100 Gm. of fat. The severity of her diabetes is indicated by total daily insulin requirements

between 110 and 140 units per day. Her most constant dose of insulin, when given as separate injections, has been 40 units of regular insulin and 80 units of protamine insulin before breakfast. She was transferred to insulin mixtures on December 8, 1943. Figure 6 is a graphic summary of one year's observation on separate injections and one year on mixtures. It will be seen that the only significant change that occurred was a marked reduction in the prandial glycosuria from 4:00 P.M. to midnight. The fasting blood sugars have remained roughly at the same level but her total insulin requirements have dropped to an average of 104 units per day and she appears to be satisfactorily controlled with a mixture of 80 units of regular insulin and 24 units of protamine insulin. This is a ratio of 4:1.

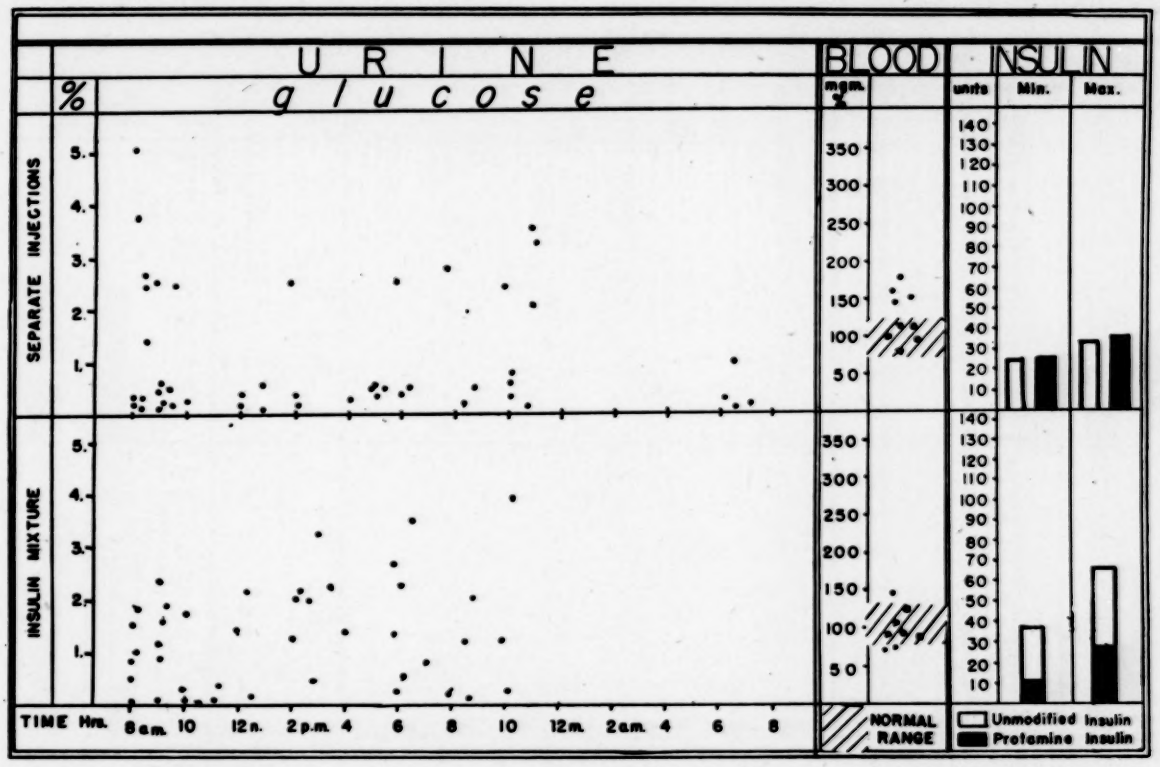


FIG. 5. Graphic summary of a nineteen year old male diabetic (Case II in the text), comparing the laboratory status for one year on separate injections of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the blood sugars are more frequently normal on insulin mixtures but that there has been no change in the intensity of the glycosuria.

CASE IV. M. R. is a twenty-one year old male who has been diabetic since the age of sixteen and came under our observation one year after the onset of his diabetes. He is a severe diabetic and has been clinically well on a diet averaging 300 Gm. of carbohydrate, 120 Gm. of protein, and 100 Gm. of fat. He is five feet ten inches tall and his average weight was approximately 160 pounds. His maintenance insulin dose averaged 20 units of regular insulin and 60 units of protamine insulin when given as separate injections. He was transferred to mixtures on December 20, 1943. It will be seen in Figure 7 that there occurred a marked reduction in the prandial glycosuria, which appeared to be especially significant after 2:00 P.M. The fasting blood sugars have been about the same on both regimens. His average maintenance dose on mixtures has been 88 units daily, consisting of 64 units of regular insulin and 24 units of protamine insulin. This is a ratio of almost 3:1. The only additional difference in his condition is that he has gained twelve pounds since he has been on mixtures. He has experienced many more insulin reactions since he has been on mixtures than on

separately injected doses and the reactions have occurred in the afternoon between 3 and 6 P.M. The patient claims a better sense of well being on mixtures and, in spite of the greater frequency of reactions, prefers to continue on this mode of treatment because it saves an injection and because he feels better.

performed on April 2, 1944, gave a typical diabetic curve. On April 23, 1944, the patient was transferred to insulin mixtures. His fasting blood sugars have continued to be normal. His glycosuria has improved markedly so that he is either sugar-free or excreting traces of sugar in the urine. It is interesting that the dose

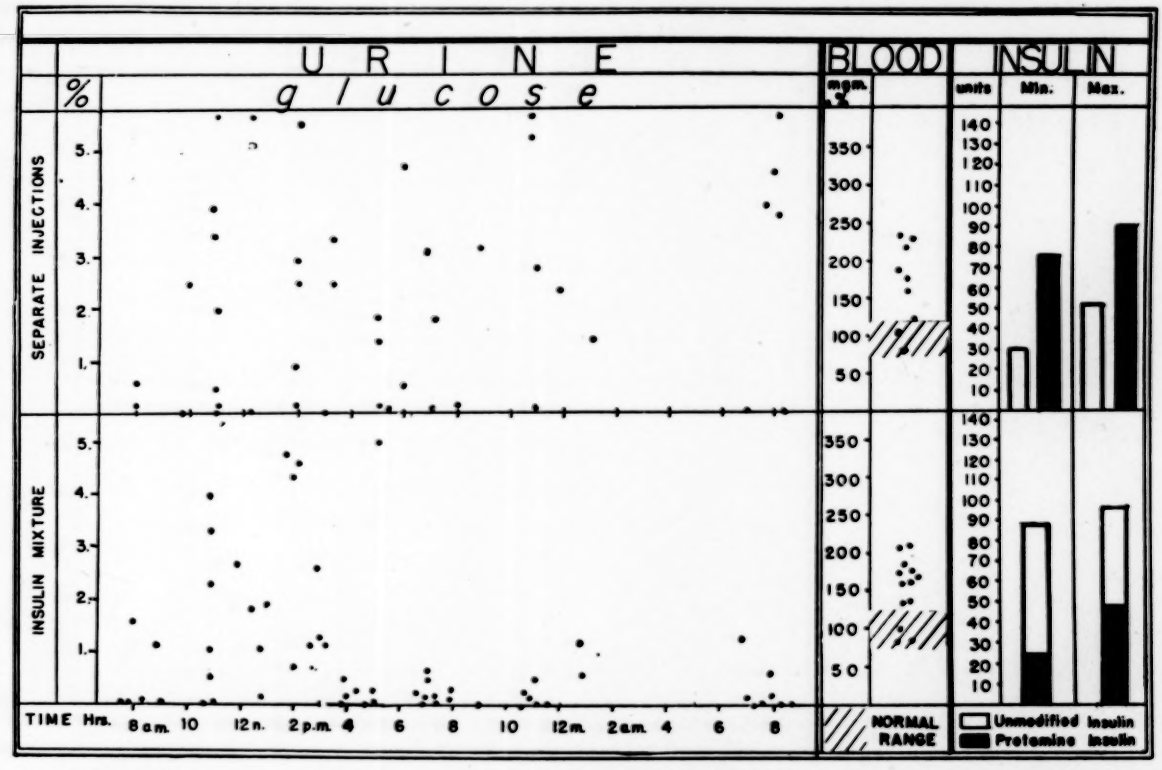


FIG. 6. Graphic summary of a twenty-one year old female diabetic (Case III in the text), comparing one year of treatment with separately injected doses of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that there was a marked reduction in prandial glycosuria from 4 P.M. to midnight on insulin mixtures. The fasting blood sugars under both conditions were approximately the same. Note also that there has been some reduction in the total insulin dose on mixtures.

CASE V. I. H. is an unusual case and is one of the few patients under observation in whom the insulin dose when given by separate injections required, for satisfactory maintenance, the administration of a larger dose of unmodified insulin than of protamine insulin. This became obvious as a result of the fact that he had almost continuous glycosuria while the blood sugar remained normal even when he received 40 units of unmodified insulin and 25 units of protamine insulin by separate injections. Some doubt even developed whether this patient was a diabetic in spite of the history of the onset of the disease with classic symptoms. A glucose tolerance test

of insulin mixtures necessary to maintain this patient satisfactorily has consisted of 60 units of regular insulin mixed with 12 units of protamine insulin, a ratio of 5:1. Any attempt to reduce this ratio has always resulted in significant glycosuria. Although the patient has been clinically well on both regimens, he has gained fifteen pounds in weight since he was placed on mixtures.

It may be said that the diabetic whose total daily insulin requirement is less than 30 units per day is no problem in management with almost any type of insulin avail-

able. The intelligent use of a physiological diet with spaced intercibal supplementary feedings will result in satisfactory control of the mild diabetic whether a single dose of protamine insulin or globin insulin is employed in the morning, or whether unmodified insulin is used in divided doses. In such cases, however, we find the use of insulin mixtures to be ideal, for the patient is best controlled by this technic.

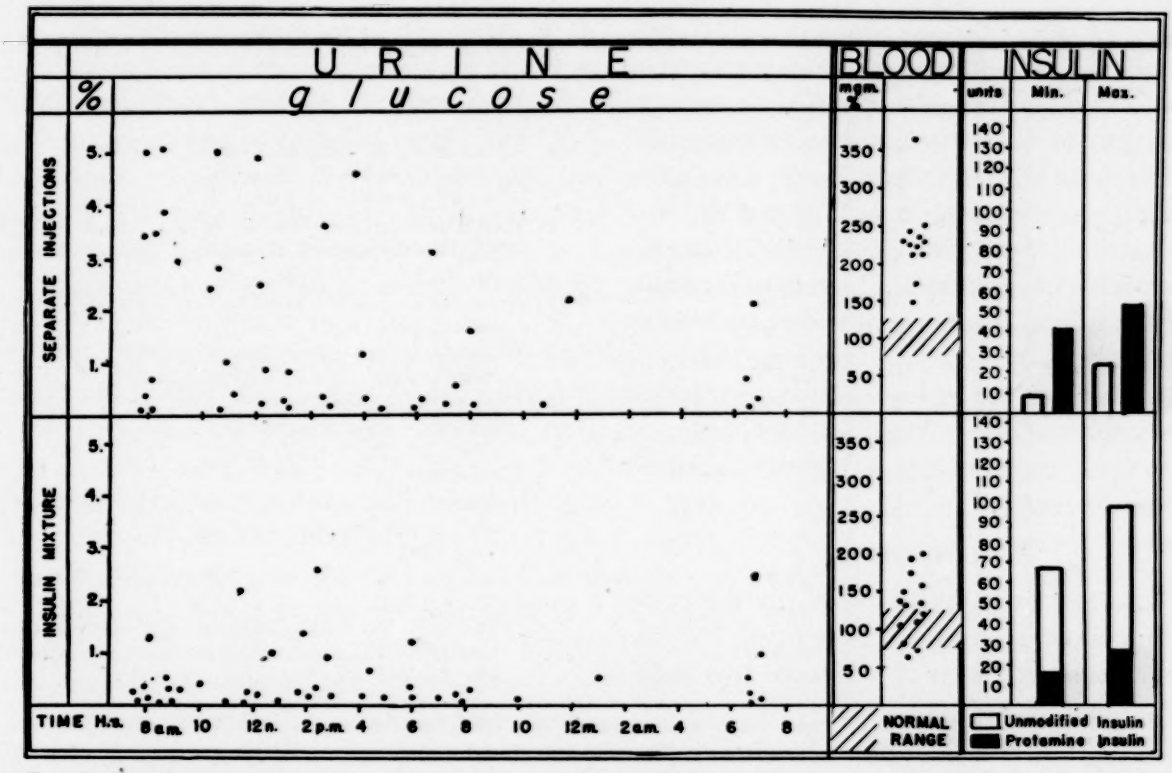


FIG. 7. Graphic summary of a twenty-one year old male diabetic (Case IV in the text) comparing one year of treatment with separately injected doses of unmodified and protamine insulin and one year on mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the prandial glycosuria is less marked, especially after 2 P.M., on insulin mixtures. Note also that the fasting blood sugars are roughly the same under both conditions.

It is the severe diabetic who presents a significant problem and in whom no satisfactory answer has as yet been obtained, even with the use of insulin mixtures.

It would appear that the use of insulin mixtures is a more desirable method of treatment in the severe diabetic than is any other previously employed technic. The important problem in the severe diabetic is to secure an insulin effect of even intensity over as much of the twenty-four hour period as possible. Although insulin mixtures are capable of accomplishing this best, the difficulty with insulin mixtures lies in their instability. As has already been indicated, the efficiency of the insulin mixture is quickly upset in the presence of any mild infection. Those who are subject to mild respiratory infections, for example, are subject to wide fluctuations in carbohydrate tolerance. Thus, the ability to maintain a patient in a zone of satisfactory clinical control, allowing him to excrete a minimal quantity of dextrose and to maintain his fasting blood sugar close to the normal level, at the same time keeping him free from hypoglycemic reactions, can be accomplished sometimes only with much difficulty.

In this series of 150 cases, we were compelled to terminate the use of insulin mixtures in four cases because these patients experienced too many insulin reactions and could not be satisfactorily controlled.

We found it necessary also to interrupt, temporarily, the use of insulin mixtures in diabetics who became pregnant. The progressive alteration in carbohydrate tolerance with advancing pregnancy is such as to make the use of insulin mixtures undesirable. These patients have been better controlled with the use of separately injected doses of unmodified and protamine insulin during the period of gestation, allowing to return to insulin mixtures one month after childbirth. Similarly, it has often become necessary to interrupt the use of insulin mixtures in patients with severe infections and to revert to separately injected insulins until subsidence of the infection.

CONCLUSIONS

An analysis is presented of the use of insulin mixtures in the treatment of 150 diabetics observed over a period of two years. The advantages and disadvantages of this method are discussed.

REFERENCES

1. Leyton, O. Administration of insulin in suspension. *Lancet*, 1: 756, 1929.
2. Gray, P. A. Treatment of diabetes mellitus with insoluble insulin compounds. *Endocrinology*, 20: 461, 1936.
3. Jacobs, H. R. and Ricketts, H. T. Retarded and prolonged action of insulin precipitated by safranon. *Proc. Soc. Exper. Biol. & Med.*, 35: 473, 1936.
4. Rosenthal, L. and Kamlet, J. Studies on alum-precipitated insulin. *Proc. Soc. Exper. Biol. & Med.*, 36: 474, 1937.
5. Hagedorn, H. C., Jensen, B. N., Krarup, N. B. and Wodstrop, K. Protamine insulinate. *J. A. M. A.*, 106: 177, 1936.
6. Bauman, L. Globin insulin. *Bull. New England M. Center.*, Feb., 1943.
7. Graham, G. Use of mixture of ordinary and protamine insulin. *Acta med. Scandinav.*, 90: 54, 1938.
8. Ulrich, H. Clinical experiments with mixtures of standard and protamine zinc insulins. *Ann. Int. Med.*, 14: 1166, 1941.
9. Colwell, A. R., Izzo, J. L. and Stryker, W. A. Intermediate action of mixtures of soluble insulin and protamine zinc insulin. *Arch. Int. Med.*, 69: 931, 1942.
10. Peck, F. B. Action of insulin. *Proc. Am. Diabetes A.* 2: 69, 1942.
    Peck, F. B. Approximate insulin content of extemporaneous mixtures of insulin and protamine zinc insulin. *Ann. Int. Med.*, 18: 177, 1943.

Experience with Insulin Mixtures*

LESTER J. PALMER, M.D. *and* JOSEPH H. CRAMPTON, M.D.

SEATTLE, WASHINGTON

HAGEDORN announced his work with insulin modified by the addition of protamine in 1935. His first American publication appeared in January, 1936.[1] Following considerable further modification of the original formula, this insulin was approved as protamine zinc insulin for commercial distribution and became available in this form in January, 1937.

Clinical use of this insulin showed that it had many advantages. The most important of these were that the insulin effect persisted for twenty-four hours or longer after a single injection and that continuous insulin influence was maintained. But it had shortcomings. The degree of insulin effect varied at different times during the twenty-four-hour period. There was the minor effect during the first few hours following injection and failure to control the post-prandial rise of blood sugar in a considerable number of diabetics. This latter weakness particularly was manifested in that group of patients with a total insulin requirement greater than 30 to 40 units per twenty-four hours.

As a result of these shortcomings a search for further modification of the formula of standard protamine zinc insulin became inevitable. Many such modifications have been given a trial; a number of these have been listed, with the modified formulas, in publications by Peck[2] over the past four years. Until the present time no modification of the formula of standard protamine zinc insulin has been evolved which excelled sufficiently in controlling hyperglycemia to justify endorsement by the Toronto Insulin Committee. Thus, no modification or replacement of current standard protamine zinc insulin has been approved.

Since the timing effect of the action of any insulin is dependent upon the pharmacological formula, it is evident that change of the formula will alter this particular feature of the action. Hagedorn suggested this at the time of his original announcement. Since no change in the standard formula of protamine zinc insulin has been acceptable to those charged with the responsibility of approving types of insulin, it was natural that alteration of the timing effect be attempted by clinicians by new methods of use of the commercially available insulins. As early as 1938,[3] reports began to appear in the literature concerning these efforts as they pertained to mixtures of quick-acting and slow-acting insulin.

Since this is a report of clinical experience with mixtures of insulin, the authors will not enter into the discussion regarding the pharmacological changes which occur when solutions of zinc insulin crystals and standard protamine zinc insulin are thoroughly mixed. These changes have been discussed extensively by Peck,[2] Colwell,[4] MacBryde[5] and others. However, it is evident from the formulas of these two insulins (Table 1) that when a mixture is made the chemical proportions and the pH change, resulting in an alteration in the pharmacological effect. It is also obvious that these changes vary, dependent upon the proportions of the mixture.

This study differs in some respects from most of those previously reported. Our observations were made almost entirely

* From The Mason Clinic, Virginia Mason Hospital, Seattle, Washington.

upon patients seen in office practice. None were under prolonged observation in the hospital. Patients were chosen for mixtures, without selection, from those who required both quick-acting insulin and slow-acting insulin to obtain satisfactory control during

TABLE I

Insulin	pH	Zinc Mg./100 Units	Protamine Mg./100 Units
Crystalline	3.0	0.02	0
Protamine zinc	7.2	0.2	1.25
Crystalline / Protamine zinc 2:1	5.9	0.67	0.42

the waking as well as during the sleeping hours. Practically all patients required insulin in excess of 30 units. (Table II.) Of course, only patients sufficiently intelligent to understand the technic of making mixtures were allowed to use them. In mixing,

TABLE II

Type of Diabetes	Total No. Patients	Average Total Insulin per Day Units
Juvenile	72	53
Adult	156	46

insulins of the same strength and of the same manufacturer were always employed.*

METHOD

When control as nearly satisfactory as deemed possible had been established on certain doses of crystalline insulin and protamine zinc insulin, the use of a syringe mixture was started. The decision as to whether to use a 1:1, a 3:2 or 2:1 proportion (the first numeral indicating crystalline insulin and the last numeral protamine zinc insulin) depended upon the number of units of crystalline and the number of units of protamine zinc insulin employed as separate injections. If the ratio of crystalline insulin to protamine zinc insulin was low, a 1:1 mixture was employed at first and, if higher, a 3:2 or 2:1 mixture was employed. In only rare instances was a greater proportion than 2:1 used in a mixture. In a considerable number of patients studied, mixtures were necessarily changed from 1:1 to 3:2 or to 2:1 but the greatest proportion of the group ultimately used a 2:1 mixture.

After changing to a mixture the patient was observed in the office in seven to ten days. A record of urine tests at home, made before breakfast and before supper on urine which represented a bladder collection from thirty to forty-five minutes, was reviewed. The patient was then interrogated regarding reactions and subjective sense of well being. A blood sugar determination was then made two and one-half to three hours after either breakfast or the noon meal. If the findings approached the satisfactory criteria of control, no change was made in the proportions of the mixture. If night control was not satisfactory, the protamine zinc insulin effect was increased either by a change of proportion in the mixture being used, or by increase of the total number of units per dose of mixture until the night time control was satisfactory. If night time control was satisfactory and day time control was not, the proportion of crystalline insulin in the mixture was increased. If both day and night controls were unsatisfactory, the total dose of the mixture was increased or decreased, with or without a change of proportion, depending upon the indication. In order to permit any given regimen to stabilize, changes were made in the proportion of the mixture or total dosage at infrequent intervals.

The metabolic load was distributed in three equal meals and a bedtime feeding, except in children under twelve years of age to whom a mid-afternoon feeding was also

* Material for the study was supplied by Eli Lilly Company.

given. In a few younger children, a mid-morning feeding was arranged, especially if breakfast was early and lunch did not come until noon.

Diets prescribed were arranged according to our usual custom and represented the basal requirements for age, height and ideal weight plus 25 to 30 per cent, except in children to whom 1,000 calories for the first year plus 100 calories for each additional year were allowed. During adolescence the total calories were 2,200 to 2,300. The ratio of Gm. of carbohydrate to Gm. of fat most often was 2:1, and all diets were liberal in protein. Carbohydrate ranged from 165 Gm. to 180 Gm. and rarely exceeded 200 Gm. except for hard labor or during convalescence. Fat was raised or lowered in accordance with the weight curve.

CRITERIA OF CONTROL

The criteria of satisfactory control were as follows: (1) sugar-free or nearly sugar-free tests of urine accumulated in the bladder thirty to forty-five minutes before breakfast and before supper; (2) blood sugar levels of 100 to 140 mg. per 100 cc. before the noon meal, or not exceeding 200 mg. per 100 cc. two hours after the noon meal.

RESULTS

Tables III and IV show by decade the age of the patient during the period of observation and the duration of the diabetes. Table V shows that as the total number of units of insulin increased the proportion of crystalline to protamine zinc insulin increased. Table VI shows the degree of control on separate injections, syringe mixtures and bottle mixtures.

These patients all used successively crystalline insulin and protamine zinc insulin (1) injected separately, (2) mixed thoroughly in a syringe immediately before injection and (3) premixed in a bottle. Therefore, it was possible to make a comparison for better or worse of the control obtained on one arrangement or the other. In grading the control of this group of patients while under one of the preceding methods of insulin administration as compared with another, it was evident that the highest percentage of patients were classified as under excellent control while using the bottle mixture.

Patients who use both crystalline insulin and protamine zinc insulin before breakfast are all anxious to use a mixture because of the simplicity and comfort of a single injection rather than two separate penetrations. Although this feature may be of interest to the clinician, if it is the only advantage of a mixture it is relatively inconsequential.

TABLE III

Age in Years at Time of Study									
0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Total
13	46	37	32	21	44	26	7	2	228 patients

TABLE IV

Duration of Diabetes

Type of Diabetes	Duration in Years						
	0–4	5–9	10–14	15–19	20–24	25–29	30–34
Adult	48	62	20	17	6	2	1
Juvenile	38	11	11	8	4	0	0

TABLE V

Type of Diabetes	Proportion of Mixture	Total Dose of Insulin per Day Units							
		10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89
Adult	1:1	0	14	18	7	1	3	0	1
	3:2	0	13	13	17	8	5	2	1
	2:1	0	6	17	17	4	7	1	0
Juvenile	1:1	1	1	0	1	2	0	1	0
	3:2	1	1	2	4	4	3	3	2
	2:1	0	2	9	10	5	9	9	1
	3:1	0	0	0	0	1	0	0	0

The most satisfactory insulin arrangement will be that which will give the most ideal control of the blood sugar throughout the twenty-four-hour period with the least number of injections and with the least deviation from the usual number of meals and their respective food values. It is our impression at present that this is more satisfactorily accomplished by a mixture than it is by separate injections. Although it is true that the greatest percentage (78 per cent) of patients selected for the administration of mixtures seems, at present, to have the most satisfactory control on the 2:1 or the 3:2 proportion, it is possible to adjust the pharmacological action of the mixture to the individual patient by changing the proportions.

TABLE VI

Type of Diabetes	Control with Separate Injections and with Mixtures			
	Comparison of Results	Separate Injection, Per Cent	Syringe Mixture, Per Cent	Bottle Mixture, Per Cent
Adult	Excellent	33	34.9	50
	Good	51	44.9	36.1
	Poor	16	20.2	13.9
Juvenile	Excellent	15.8	15.5	36
	Good	55.6	49.3	36
	Poor	28.6	35.2	28

Further study of mixtures is indicated by the success of those who have employed them and have reported to date. More extensive data are necessary for full evaluation. It is expected that mixtures will be studied more widely in the diabetic clinics of the country in the next year or so. The decision as to whether mixtures will remain as a procedure in the care of diabetes in the future, or whether from these studies will come data which will be the basis of a new formula for a slow-acting, long-acting insulin to replace the present standard protamine zinc insulin, will remain with the Toronto Insulin Committee. It would seem that such future decisions will be aided by studies of this kind.

SUMMARY

1. The data obtained by office observation of 72 juvenile and 156 adult diabetics while on syringe or bottle mixtures of crystalline insulin and standard protamine zinc insulin have been presented.

2. In general, mixtures either extemporaneous in the syringe or premixed in a bottle have proven to be a satisfactory method of administration for those patients requiring both quick-acting and long-acting insulins.

3. The data seem to suggest a preference for bottle mixtures.

REFERENCES

1. HAGEDORN, H. D., JENSEN, B. N., KRARUP, N. B. and WODSTRUP, I. Protamine insulinate. *J. A. M. A.*, 106: 177–180, 1936.
2. PECK, F. B. Action of insulin. *Proc. Am. Diabetes A.*, 2: 69, 1942. PECK, FRANKLIN B. Approximate insulin content of extemporaneous mixtures of insulin and protamine zinc insulin. *Ann. Int. Med.*, 28: 177, 1943. PECK, F. B. and SCHECTER, J. S. The newer insulin mixtures. A follow-up study. *Proc. Am. Diabetes A.*, 4: 59–86, 1944.
3. GRAHAM, GEORGE. Use of a mixture of ordinary and protamine insulin. *Acta med. Scandinav.*, 90: 54, 1938. LAWRENCE, R. D. and ARCHER, NORA. Zinc protamine insulin; a clinical trial of a new preparation. *Brit. M. J.*, 1: 487, 1937. UHLRICH, A. Clinical experiments with mixtures of standard and protamine zinc insulins. *Ann. Int. Med.*, 14: 1166, 1941.
4. COLWELL, A. R. Nature and time action of modifications of protamine zinc insulin. *Arch. Int. Med.*, 74: 331–345, 1944.
5. MACBRYDE, C. M. and ROBERTS, H. K. Modified protamine zinc insulin: improvement on standard protamine zinc insulin. *J. A. M. A.*, 122: 1225–1231, 1943. MACBRYDE, C. M. and REISS, R. S. Modified protamine zinc insulin: comparison with globin zinc insulin and insulin mixtures. *J Clin. Endocrinol.*, 4: 469–479, 1944.

Myasthenia Gravis and Spontaneous Curarism*

Lipidystrophy as Possible Cause

R. DE ROHAN BARONDES, M.D.†

LOS ANGELES, CALIFORNIA

In spite of extensive study, insight into the etiology of myasthenia gravis is still lacking. As the name implies, the disease manifests itself in a state of profound weakness of the muscles, those of the eyes, face and throat, as a rule, being involved first. The affected muscles show large collections of lymphocytes among the fibers which neither deteriorate nor atrophy nor do they show the reaction of degeneration. When these muscles are stimulated by faradic current, repeated at intervals of seconds, the muscular contractions become weaker with each stimulation and soon disappear. The thymus gland is frequently found enlarged, its activity being related in some manner to the lymphocytic infiltration of the muscle.

Preliminary data show that some marked fault in lipid metabolism may be an initiating factor through the release into the tissues of a lipid-cleavage product with curare effect. Some of these products also exert positive chemotaxis on the lymphocytes, the collections of lymphocytes among the muscle fibers being correlated with the observation that the lymphocyte possesses a special lipolytic enzyme to break down alien lipid material. The typical curare action consists essentially of an interruption of nerve impulses to muscle. This interruption takes place at the termination of the nerve fibers at the muscle cells. This effect probably consists in a neutralization of the acetylcholine reaction which constitutes the fundamental neuromuscular stimulation mechanism.

Myasthenia is accompanied by a high degree of creatinuria and a reduction in creatinine. Administered creatine is practically all excreted as such apparently through failure to store it properly. Glycine is the precursor of creatine, the site of production of the latter being in the muscle. Muscle hypoglycinosis in myasthenia no doubt results from too rapid conversion of glycine to creatine, for the feeding of glycine stimulates creatine excretion. A correlation exists between glycine breakdown and creatine excretion. Its appearance in the urine after glycine tolerance tests is of great diagnostic value in myasthenia, muscle atrophies of the Charcot-Marie type, progressive muscular atrophy, congenital and other myotonias and also in the exanthemata, prolonged fevers, etc. Glycine is normally involved in the intermediary metabolism of carbohydrates and it increases the oxygen capacity. It also serves, like sulfhydryl, in cellular respiration, in the biological phenomena of oxidation-reduction, and in detoxifying processes of the body. In these toxic states there is a considerable drain upon the glycine and sulfur stores for detoxication purposes which leads eventually to such deficiencies.

Although remissions occur in myasthenia,

* The opinions or assertions contained herein are the private ones of the author and do not necessarily reflect the views of the Veterans Administration.

† From Veterans Administration Hospital, Los Angeles, Calf.

death eventually results from paralysis of the respiratory muscles. The disease is often relieved during pregnancy but returns after delivery, the improvement being associated with improvement in creatine metabolism and the increased body lipid level. Creatine is normally found in the blood plasma in pregnancy and in the young in whom both plasma creatine and phospholipid values are high. From birth to puberty creatine is excreted but thereafter creatinuria is abnormal. Creatine is found in brain tissue, gray matter being far richer than the white matter. It is considerably increased in the blood of catatonic patients showing marked rigidity, whereas low creatine values are found in deteriorating dementia praecox and involutional melancholia.[1] In many brain and nerve disorders, the tissues also show lymphocytic infiltration which is apparently the result of abnormal lipid metabolism and disturbances in creatine and glycine metabolism.

A recent concept of myasthenia is that the fundamental disorder is not primarily in the central nervous system but in the motor fibers of the peripheral nerves and the muscle end plates where acetylcholine is liberated and then destroyed by the enzyme cholinesterase. There is also some evidence that the enzyme choline-acetylase, which synthesizes acetylcholine under anaerobic conditions, is inactivated by some toxic agent to prevent acetylcholine synthesis, the muscle then becoming refractory to cholinergic stimulation. The myoneural junction interposed between nerve fiber and muscle is a region in which conductivity is difficult and readily modified, so that it may be the seat of summation, inhibition and fatigue. The depression of cholinesterase activity, therefore, would be an important accompaniment of therapeutic improvement in muscles which have become refractory to cholinergic stimulation.

Ordinarily, the transmission of nerve impulses at the myoneural junction depends on the liberation of acetylcholine, $C_7H_{17}NO_3$, an important lipid component. In myasthenia there is either an insufficiency through failure in acetylcholine synthesis or else it is rapidly destroyed by cholinesterase at the myoneural junction. Normally, stimulation at the motor nerve endings in voluntary muscle causes the liberation of acetylcholine which induces muscular contraction. As each nerve impulse transmitted along a preganglionic fiber causes but one impulse to be discharged along the postganglionic fiber, it is assumed that a fresh quantity of acetylcholine is liberated by each preganglionic impulse and is then destroyed by the action of cholinesterase. It is generally accepted that acetylcholine is liberated from the nerve terminals rather than from cells in relation to them, but whether or not it is liberated from a preformed store or is synthesized by the nerve impulse is not known. The brevity of time available for such a process speaks against the latter mechanism. Acetylcholine production may not keep pace with the concentration of cholinesterase although in myasthenia this enzyme is not found to be above normal concentration. Acetylcholine has great physiological importance as a parasympathetic stimulant but the ease with which it is hydrolyzed to inert choline and acetic acid prevents its extensive therapeutic use.[1]

It is not within the scope of this paper to discuss as complex a subject as the phenomenon of nerve-impulse transmission but rather to point out some morbid metabolic disturbances of the body lipids that may have an important bearing on the genesis of myasthenia gravis.

LIPIDYSTROPHIES

The important lipids such as the phospholipids, lipoproteins, glycolipids, lecithin, cephalin, sphyngomyelin, the cerebrosides, etc., are found extensively throughout the

animal and vegetable kingdoms. They are present in the human body in much larger amount in the brain and nerve tissue than elsewhere. The lipid values decrease during fasting, acidotic states, anoxia, etc., and are adversely affected by certain enzymes and hormones; insulin and thyroxin decreasing the lipid values. In fatigued muscle the lipids become greatly reduced, with an increase in ammonia probably arising from lipid breakdown.

In general, the lipids act as agents for the transport of oxygen within the cells and serve also as supplementary or intermediary agents (co-enzymes) to activate various enzymes. They also exert a protective effect against bacterial and viral toxins. The antioxidant lecithin plays an important rôle in cellular activity and the transfer and metabolism of fatty and carbohydrate material in the body. It is concerned in the metabolism of vitamin A, $C_{20}H_{30}O$, an unsaturated aliphatic alcohol which is synthesized from carotene and a chromolipid hydrocarbon, $C_{40}H_{56}$. Vitamin A increases the serum lipid level, acting as an oxidation-reduction catalyst to influence the utilization of lipid material. Avitaminosis-A, by causing hypolipidosis and abnormality of the lipids, results in a condition resembling subacute combined degeneration of the spinal cord. Lack of this vitamin also causes inadequate production and regeneration of the chromolipid visual purple in the retinal rod cells and thus causes night blindness. With this condition there is noted vasoconstriction of the retinal arteries and an accompanying photophobia through some little understood photochemical effect that disturbs the acid-base balance.[3] Illumination of the eyes causes bleaching of visual purple and an alteration in the pH from alkaline to acid; the pH of the retinal tissue falling further as the light intensity is increased. Certain dietary lipid-deficiency symptoms resemble those induced by vitamin A and E deficiencies and can be alleviated by the administration of such fatty acids of animal lipid origin as linoleic, stearic and arachidonic acids. The latter, $C_{20}H_{32}O_2$, conceivably is synthesized to vitamin A. Favorable effects have been reported through use of vitamin E in some of the myopathies with improvement in creatine metabolism.

The lipids are more or less unstable and in certain morbid processes readily undergo derangement and breakdown with the release of numerous toxic degradation products. Some of these lipid cleavage products are highly lytic while others exert curare-like effects. A third group of such products exert selective tetanic effects upon the synapses to lower synaptic resistance and convert inhibition into active contraction. The latter morbid effects are observed in both tetanus and rabies infections where the toxigenic enzymes of these pathogens under anaerobiosis selectively seek from the nerve tissue such lipid components as lecithin, acetylcholine, choline, neurine, etc., to break down to cleavage products of highly tetanic nature. The progressive enzymic decomposition of these nerve bases along appropriate nerve tracts would explain the manner in which these toxins, reach the brain to produce the symptoms of the disease.[2] The recognized therapy of these two diseases if instituted early inhibits the production of tetanus and rabies toxins, an effect like that of extinguishing a fuse to prevent a disastrous explosion. The muscle rigors in both diseases cause excess production of organic acids, such as lactic acid, that further cell fluid absorption, spasmodic contraction and nerve irritation. Another factor in the muscle rigors is the increased output of acetylcholine at the myoneural junction and the inactivation of cholinesterase which normally serves to destroy acetylcholine but is itself inactivated by the changed pH of the tissues. Eventually, the hypothalamus and cerebral cortex become

affected, seriously interfering with the fronto-pontine tracts conveying impulses that normally serve to release muscular rigidity.[2]

When the lipids are acted upon and lose a fatty acid group, highly hemolytic substances such as lysolecithin, lysocephalin and lysosphyngomyelin are formed. These lysolipins are capable of lysing cells through their great affinity for water and other fluids which on entering the cells cause swelling and rupture of the cell membranes. The more acid these fluids become the greater is the cell imbibition. The lysolipins combine readily with cholesterol, molecule for molecule, such combinations then becoming antitoxic agents with no further lytic power. Cholesterol, in addition to its protective action against cell lysis, is also concerned with the body's reaction to infectious diseases and with the processes of immunity.

SPONTANEOUS CURARISM

Several investigators have suggested the possible presence in the blood or tissues of myasthenic patients of some toxic substance that blocks synaptic transmission, raising the threshold of skeletal muscle to the effect of acetylcholine.[4-7] However, such a toxic agent has eluded detection.

Recent study tends to show that a myoneural toxin is a major factor in the etiology of myasthenia gravis and that it is a cleavage product resulting from some abnormality in the cell lipids. The quaternary ammonium compounds such as acetylcholine, choline and other components of lipids like sphingosine and stearamide are the precursors of several myoneurotoxins. Acetylcholine induces muscular contraction and some of its derivatives often cause severe muscle hypertonicity. Other toxins similarly derived exert curare-like effects. The latter effect no doubt is dependent upon the pentavalent nitrogen, or rather the stereochemic orientation of the valences, while the hypertonic effects depend upon different orientations. These imply phenomena that are rather difficult to explain fully upon biochemical grounds. The choline-derived myoneural toxins with curare-like effect, such as botulinine, mytilotoxin, muscarine and coniine, and the similarly acting tetramethyl-ammonium bases such as guanidine and methyl-guanidine interrupt the nervous impulses at the termination of the nerve fibers at the muscular cells. Sphingosine, $C_{18}H_{37}NO_2$, an important amino alcohol, is a component of sphyngomyelin, the latter also being composed of choline and the fatty stearic acid radical. Its stearamide, $C_{18}H_{37}NO$, and the anhydride, stearonitrile, $C_{18}H_{35}N$, bear close structural relationships to curarine ($C_{18}H_{35}N$) if not having similar effects. Under what conditions nitriles may be formed from amines and amides is yet to be discovered.

What may be of considerable significance in myasthenia are the large collections of lymphocytes among the muscle fibers. These are usually indicative of the presence of toxic or alien lipid material, being correlated with the presence in the lymphocyte of a special lipolytic enzyme capable of breaking down morbid lipid products. These lipid products are positive chemotactic agents that cause attraction of the lymphocytes. Local collections of lymphocytes usually occur in and about lesions caused by bacteria that contain lipid material, notably the tubercle and lepra bacilli. These pathogenic agents are well protected by their lipid waxy capsules, surviving even in 15 per cent concentrations of sulfuric acid that will kill all other bacteria. The lipolytic enzymes of the lymphocytes are capable of completely lysing the waxy material if not inactivated by the accumulated cleavage products of their enzymic activities.

CURARE AGENTS

Drugs with curare action counteract the effects of spasm-producing agents by increasing the refractory period. Magnesium

compounds, quinine, nicotine, lobeline, gelsemium, coniine, muscarine, guanidine, methylguanidine and erythroidine exert depressant action on the peripheral ends of the motor nerves to control muscle spasm. Atropine prevents spasm apparently by acting upon the effector cells and antagonizing acetylcholine but does not prevent its liberation at the nerve terminals. In botulism and mussel and conium poisoning the absorbed preformed choline-derived alkaloids exert curare-like effects upon the nerve endings in the parasympathetic system. These toxins produce typical myasthenic symptoms and cause degenerative changes in the motor cells of the medulla and spinal cord not unlike those observed in poliomyelitis, acute encephalitis and other conditions which arise from certain viral infections. The toxins formed by the neurotropic viruses probably result from the interactions of their enzymes with specific nerve and brain lipid components susceptible to their influences.

Curarine, the active principle of curare, exerts a specific effect upon the motor endplates by raising the threshold of skeletal muscles to the effects of acetylcholine. Death is caused through paralysis of the respiratory muscles by the blocking of the passage of nerve impulses across the myoneural junction. Curare also lowers the output of epinephrine from the suprarenal gland and has been used in the treatment of certain hypertensive states that result from hyperadrenia. It has considerable therapeutic value in the early muscle spasms of poliomyelitis, athetosis, tetanus, rabies, maniacal outbursts, myoclonias and hypertonic states, convulsions and arachnidism, as well as counteracting the effects of spasm-producing drugs such as strychnine and metrazol. Strychnine has a marked affinity for cholinesterase, destroying its activity and permitting acetylcholine to exert its full stimulatory effect at the motor nerve endings.

In curare poisoning the muscles least affected are those which contain the largest amount of utilizable oxygen, these surviving the longest after death of the animal. Any myopathy that causes lowered oxygen supply prevents fatigued muscle from obtaining oxygen necessary to its recuperative powers; such tissue is then rendered more likely to be susceptible to the depressing effect of curare. Myasthenic cases are extremely sensitive to curare (this hypersensitivity being utilized in a two-minute diagnostic test for myasthenia gravis) since one-fifteenth to one-fifth of the average dose (Intocostrin*) given intravenously produces a profound exaggeration of symptoms and may add new symptoms not previously exhibited in a myasthenic patient.

The effects of curare are counteracted by the quaternary ammonium compound physostigmine which stimulates the myoneural junction. Physostigmine and like compounds might provide a biochemical means of counteracting the myoneural toxins of botulism, mussel poisoning and certain mushroom poisonings that exert curare effects. Neostigmine causes dramatic improvement in myasthenia gravis by augmenting the effect of acetylcholine, stimulating the myoneural junction and temporarily depressing cholinesterase activity. What effect it might exert on the lipolytic activity of the lymphocytes has yet to be determined. The effect of one injection persists about eight hours and may be prolonged if given in a vehicle to lessen the rate of systemic absorption. The action of physostigmine preparations is enhanced by glycine, ephedrine, antuitrine benzedrine, acetylcholine and potassium salts, the latter ions serving to stimulate the ganglion cells and increase acetylcholine production. Neostigmine and curare are of therapeutic value in relieving the early muscle spasms of poliomyelitis. Although their physiological effects are

* Squibb purified extract of curare.

opposed to one another, they relieve muscular spasticities probably by acting upon the synapses in the spinal cord to decrease fatigue, increase muscle tonus and relieve pain.

CONCLUSIONS

1. The primary disturbance in myasthenia gravis may be a lipidystrophy resulting from an abnormality in lipid metabolism. Through a fault in the cellular metabolism of such lipid components as choline, acetylcholine and sphingosine a myoneural cleavage product with curare-like action is released in the tissues. Transmission of the motor impulse at the myoneural junction is then blocked, raising the threshold of skeletal muscle to the effect of acetylcholine.

2. There is a migration, infiltration and collection of lymphocytes in the muscle fibers in myasthenia gravis. The lymphocyte possesses a lipolytic enzyme capable of breaking down alien lipid derivatives.

3. Glycine is the precursor of creatine, which is produced in muscle where it is chiefly stored for proper muscle tonus. Creatinuria is an index of abnormal glycine breakdown in myasthenia and other myopathies.

REFERENCES

1. Best and Taylor. Physiologic Basis of Medical Practice. Baltimore, Williams & Wilkins Co.
2. Barondes, R. de R. Experimental pathobiology. Research Faculty of Medicine, University of Paris, France. 1922–1923.
3. Barondes, R. de R. Night blindness, treatment with vasodilators. *Brit. J. Ophth.*, Ibid. *M. Rec.*
4. Barondes, R. de R. Antibacterial and healing factors in wounds. *M. Rec.*, 1942.
5. Nevin, S. *Brain*, 57: 239, 1934.
6. Nevin, S. *J. Neurol. Psychiat.*, 1: 120, 1938.
7. Meredith, J. M. Myasthenia gravis, with special reference to morbid metabolism and pathology of the disease. *J. Nerv. & Ment. Dis.*, 93: 185–207, 1941.
8. Torda, C. and Wolff, H. G. Release of curare-like agent from healthy muscle and its bearing on myasthenia gravis. *Proc. Soc. Exper. Biol. & Med.*, 58: 242–246, 1945.
9. Barondes, R. de R. Leprotoxin. Induced lymphocytosis and leukocytosis in lepra and phthisiotherapy, and in certain other disorders. (In press.)
10. Barondes, R. de R. Changed pH of body tissues in disease. *Southwestern Med.*, 1942.
11. Barondes, R. de R. Role of toxic agents in genesis of pellagra and allied disorders. *Am. J. Digest. Dis.*, 1936.
12. Barondes, R. de R. Changed chemistry of brain tissue in the psychotic. *M. Rec.*, 1939, 1942.

The Jejunal Syndrome*

OTTO PORGES, M.D.

CHICAGO, ILLINOIS

THE wider use of partial resection of the stomach for the treatment of peptic ulcer directs our attention to a disorder which was termed "dumping" syndrome by Eusterman and Balfour.[1] It has been recently discussed by Snell,[2] Glaessner,[3] Schwartz, Reingold and Necheles,[4] Jordan,[5] Miller,[6] Church and Hinton,[7] Berkman and Heck.[8] The patients become tired and sleepy after meals; they are nauseated, have a feeling of pressure in the stomach area, complain of heat and perspire abundantly. Some cases show tachycardia, fall in blood pressure, and even fainting and syncope occur. This syndrome has been explained as caused by distention of the jejunum, "dumped" with food from the anastomosed stomach, therefore the term "dumping" syndrome.

I encountered the syndrome as far back as in the twenties when studying the pathology and symptomatology of disorders of the small intestine. I followed up cases of acute enterocolitis. After subsidence of the diarrhea the feces became normal as regards their macroscopic appearance, the physical and x-ray examination of the colon did not reveal any pathology. But certain complaints and symptoms persisted pointing to the small intestines as the site of the disorder. Furthermore, I observed the same symptoms in numerous other patients without antecedent enterocolitis. I supposed this distress to be a catarrh of the small intestines.[9,10,11,12] I called it enteritis in distinction to catarrh of the large intestines, colitis. There is no anatomic confirmation of my conception, but animal experiments of Mahler, Nonnenbruch and Weiser[13] point to a frequent occurrence of enteritis. These authors gave spices such as pepper and paprika to dogs by mouth and examined the mucous membrane of the jejunum the day after. They saw a reddened, swollen mucosa with numerous ecchymoses and the villi were paralysed. As a matter of fact, the syndrome which I described as enteritis is rather frequent and, I dare say, every physician must have seen these cases although they may not be recognized but diagnosed as indigestion or nervous stomach or spasticity of the colon or some other disorder.

From the complaints of the patients, I distinguished the following groups: (1) Enteritis imitating gastritis. The patient complains of poor appetite, epigastralgia and nausea. He is sensitive to heavy food and may vomit at times after heavy meals. (2) Enteritis imitating peptic ulcer. The patient complains of colicky pains occurring a short while after eating, radiating to the left upper abdomen. These pains last only a few minutes but may recur, whereas ulcer pains last for hours. Unlike ulcer pains they are not relieved by food and alkaline drugs. (3) The syndrome described above as "dumping" syndrome. Patients in this category are rare compared with the number in the other groups of enteritis.

Physical examination in enteritis reveals tenderness of the left side of the abdominal wall at the level of the umbilicus, which I have called "jejunal pressure point." The best way of checking it is to have the patient lift himself from a supine to a semi-sitting position without support of his arms, where-

* From the Department of Internal Medicine, Northwestern University Medical School, Chicago, Ill.

upon the abdominal muscles stay contracted. Different points of the rectus muscle are pressed with the thumb and the patient is asked which one is the most sensitive. In cases of jejunitis the point to the left of the umbilicus is most sensitive. In cases of ileitis the pressure point is to the right of the umbilicus. There is a pressure point on the back to the left of the twelfth vertebra in some cases of jejunitis. The most important test for the diagnosis of enteritis is the microscopic examination of the feces. The stool may be formed. In cases associated with constipation it is hard and dry; the color may be normal, dark brown, except for severe cases who have light yellow feces. The microscopic examination reveals numerous soaps as crystals in the form of blunt needles, sometimes mixed with slender needles of fatty acids. In the healthy state, as is well known, there are hardly any soap crystals in the feces and only a few soap globules. In severe cases of enteritis with yellow feces the microscopic picture resembles that in icterus; the field is covered with soap crystals. Roentgen examination reveals accelerated passage through the small intestines in many cases of enteritis; two hours after intake barium has already reached the colon.

The increase of soaps in the stool points to impaired absorption in the small intestines. There may not be enough time for complete absorption because of accelerated transportation or there may be a functional impairment of absorption, or both. Sprue, another disease of the small intestine, is known to be accompanied by soapy feces. From this point of view, enteritis and sprue may be the same condition, differing only in the degree and extent of the impairment and probably in the etiology, the latter being associated with vitamin deficiency. Severe enteritis may turn into sprue either by failure of absorption of vitamins or because of insufficient supply of vitamins with the food, or both. Enteritis itself is, according to my experience, in no way connected with vitamin deficiency and cannot be cured by vitamin medication.

I described briefly the clinical pathology of enteritis because the same symptoms may be encountered in cases of resected stomach. Among the disorders observed in those patients is a group with epigastralgia, nausea and poor appetite, simulating gastritis. Berkman and Heck[8] describe instances of such complaints. There is another group complaining of pains radiating to the left abdomen suggesting jejunal ulcer, and finally there are cases of the "dumping" syndrome. The explanation of this last complaint as being caused by distention of the jejunum has been questioned by Berkman and Heck. While all instances of resected stomach observed by these authors revealed "dumping" of the jejunum, only 5.6 per cent of their 500 cases suffered from this symptom. Moreover, I have seen patients without resection of the stomach and without "dumping" presenting the same syndrome. The emptying of the stomach and filling of the jejunum was completely normal in these patients. The following case is an example of "dumping" syndrome without dumping.

CASE REPORT

A male, aged forty-three, had an attack of diarrhea two years ago, with six to ten bowel movements a day. After a week of bland diet, the diarrhea ceased and he has had normal bowel movements since. There was some indigestion after meals during the next weeks which became gradually worse and within two months the "dumping" syndrome developed: Tired feeling, hot flushes and perspiration after meals. At times the patient became dizzy and had to lie down. We observed him after meals and saw his face covered with beads of sweat, his shirt soaking wet from perspiration. The examination revealed an underweight man of normal skin, normal complexion, normal body build. The physical examination of the mouth and

chest organs did not show pathology. There was a tender pressure point of the left rectus abdominis at the navel level. The gastric analysis was normal. The feces were formed, light yellow. The microscopic examination revealed abundant small blunt soap crystals and some digested muscle fibers. With roentgen rays normal outlines of the stomach and intestines, normal motility and emptying of the stomach were seen. The patient took barium and right after the stomach examination a veal chop with potatoes. Two hours after taking barium one third of the barium was still in the stomach, traces were in the jejunum, and the bulk was in the ileum, cecum and ascending colon.

The attack of diarrhea at the onset of the disease very likely was acute enterocolitis. The colitis cleared up as proved by the subsidence of the diarrhea, but the enteritis continued and became worse, as indicated by the development of the "dumping" syndrome. This and other cases prove that the syndrome can occur without "dumping." But "dumping" may be an important factor after gastric resection, not so much mechanically by distention of the jejunum, but in producing enteritis. Unprepared and indigested food may be the cause of enteritis not only in cases of resected stomach, but in patients with jejunostomy as well, in which, according to observations of Alvarez[14] and other authors, the syndrome can be induced by jejunal feeding. Undigested food poured directly into the jejunum may elicit a reaction even from the normal mucous membrane of the gut. Another factor producing enteritis may be the kind of food given to resected patients before the distress started. Too hot or too cold food or drinks, spices, roughage may cause damage to the mucous membrane of the jejunum, and, if repeated, may produce jejunitis. This may explain why only some of the resected patients suffer this kind of distress. Besides there may have been enteritis before the resection of the stomach in some cases, and the "dumping" may have aggravated the disease.

All my cases of "dumping" syndrome, resected and unresected alike, revealed the signs and symptoms described above: The jejunal pressure point, increased soaps in the feces and accelerated passage through the small intestines, whereas resected patients without complaints did not show those symptoms.

According to the aforementioned observations "dumping" may not be the direct cause of the syndrome, the distress rather may be due to jejunitis, produced of course by the failure of digestion and preparation of the food in the stomach. Therefore, I would propose abandoning the term "dumping" and call it "jejunal syndrome." For the symptoms of tachycardia, drop of blood pressure, dizziness, fainting, I used the term "jejunal shock."[11,12]

As pointed out above, the jejunal syndrome is rare, whereas enteritis is a rather common disease. In the majority of cases the distress is not severe, and there are many instances with no complaints at all. Slight gastritis-like symptoms are the complaints most frequently encountered. The disease is of more importance because of complications and sequelae. Flatulence is often present. It may be caused by the accelerated passage through the small intestines, so that more undigested carbohydrates are carried into the colon and fermented there by bacteria producing gases. The disease may descend into the cecum causing tenderness of this area and later to the lower colon, whereupon diarrhea sets in. Bacteria may gain entrance into the portal circulation from the inflamed mucosa of the small intestines and may be carried into the liver and bile, infecting the gall bladder and bile passages, and cholelithiasis may result.

SUMMARY

1. The "dumping" syndrome observed in patients after resection of the stomach is a syndrome due to severe enteritis or jejunitis

and may be seen in cases without resection of the stomach.

2. Enteritis is a frequent disorder. The "dumping" syndrome is rare whereas complaints simulating gastritis or peptic ulcer are more often encountered.

3. The signs of enteritis are briefly described.

4. The use of the term "jejunal syndrome" instead of "dumping" syndrome is suggested.

REFERENCES

1. Eusterman, G. B. and Balfour, Donald C. The Stomach and Duodenum. Philadelphia, 1936. W. B. Saunders Company.
2. Snell, A. M. Behavior of stomach after operation for duodenal ulcer. *Am. J. Surg.*, 35: 45, 1937.
3. Glaessner, C. L. Hyperglycemic shock. *Rev. Gastroenterol.* 7: 528, 1940.
4. Schwartz, A., Reingold, I. and Necheles, H. Report on 230 cases of subtotal gastric resection for peptic ulcer. *Am. J. Digest. Dis.*, 9: 151, 1942.
5. Jordan, S. M. Investigation of the relationship between blood smear and general complaints following subtotal gastric resection. *J. A. M. A.*, 116: 586, 1941.
6. Miller, G. G. End results of radical surgery of the gastrointestinal tract. *Surgery* 12: 383, 1942.
7. Church, R. E. and Hinton, J. W. Follow-up results in subtotal gastric resection for ulcer. *Am. J. Digest. Dis.*, 9: 317, 1942
8. Berkman, J. M. and Heck, J. E. Symptoms following partial gastric resection. *Gastroenterol.* 5: 85, 1945.
9. Porges, Otto. Über Dünndarm Katarrh ohne Dickdarm Katarrh. *Ztschr. f. klin. Med.*, 109: 28 1928.
10. Idem. Über das klinische Krankheitsbild der Enteritis ohne Kolitis. *Wien. klin. Wchnschr.*, 44: 442–445, 1931.
11. Idem. Uber Dünndarm Katarrh ohne Dickdarm Katarrh. *Karlsbader Vorträge*, 1935, 1924.
12. Idem. Darmkrankheiten, 2. Aufl. Wien, 1938. Urban and Schwarzenberg.
13. Mahler, P., Nonnenbruch W. and Weiser, J. Beiträge in Physiologie, Pharmakologie und Pathologie der Dünndarm Dotten beim Hund und beim Menschen. *Ztschr. f. d. ges. exper. Med.*, 85: 71, 1932.
14. Alvarez, Walter C. An Introduction to Gastroenterology. New York, 1940. Hoeber.

The Use of an Injector Meter for Maintenance of a Prescribed Oxygen Concentration and Elimination of Carbon Dioxide in Closed Head Tents*

ALVAN L. BARACH, M.D.

with the technical assistance of Eva Levenson, B.A. and Charles C. Rumsey, Jr.

NEW YORK, NEW YORK

THE open box for administration of oxygen, originally described by Burgess,[1] was subsequently modified by him and his collaborators by closing the top of the tent with a rubber cover in order to administer high concentrations of oxygen.[2] The carbon dioxide was at first removed by soda lime contained within the apparatus, the heat and moisture by an ice rack. Later, Saklad and Burgess[3] used an injector from the oxygen cylinder to circulate the oxygen enriched atmosphere through a soda lime container outside the tent. Since employment of soda lime requires frequent testing of carbon dioxide concentrations within the tent, it seemed more convenient to use an injector attached to the regulator to furnish sufficient oxygen and outside air to wash out the carbon dioxide given off by the patient.

In large tents with motor-blower circulation, a flow of 15 liters per minute for twenty minutes, with a maintenance flow of 10 liters per minute, is generally adequate to maintain an oxygen concentration of 50 per cent and reduce the carbon dioxide concentration below 1 per cent. This is made possible by the fact that a considerable diffusion takes place under the canopy at its contact with the bed clothes and through the mattress.

In the closed head tent there is virtually no entrance of gas into the tent other than that being delivered from the oxygen regulator. Thus, with a patient who is eliminating 200 cc. of carbon dioxide per minute, a flow of 20 liters of gas per minute would be required to dilute the exhaled carbon dioxide to a percentage level of approximately 1 per cent. If pure oxygen were run into the tent at this rate of flow, the percentage in the tent would soon reach 95 per cent or more. With the use of the injector, however, large volumes of gas may be admitted into the tent without the need for large oxygen flows and with percentages of oxygen in the inhaled atmosphere corresponding to those set by the injector, as produced in the Meter mask assembly.[4]

TABLE 1

Percentage Setting	Air Intake per Liter of Oxygen Flow
40	3.14
45	2.28
50	1.72
60	1.02
70	0.61
80	0.34
90	0.14

A Meter, i.e., injector, will mix a definite

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City. This report is part of a study made possible by a grant from the Linde Air Products Company and from Mr. Cornelius Crane.

volume of air with oxygen depending on the percentage setting. These volumes are shown in Table I. To obtain a total gas flow of 20 liters per minute with a 40 per cent mixture, a flow of only $\frac{20}{1 + 3.14}$, approximately 4.8 liters per minute of oxygen is required. Under these conditions the oxygen concentration in the closed head tent would be very close to 40 per cent.

We have listed the height, weight and age of various groups of patients in Table II. The oxygen flow rate requirements for various oxygen percentages for these groups are likewise listed. With these suggested flows the carbon dioxide levels in the tent will be approximately 1 per cent. If lower or higher carbon dioxide levels are desired, increase or decrease the suggested oxygen flow rates by the following formula:

$$\frac{\text{Oxygen flow rate} \times 1}{\text{CO}_2 \text{ percentage desired}}$$

To use this chart determine the age, height and weight of the patient. If fifteen years or under, choose nearest height, weight and age category (first three lines in Table II) and read flow requirements on this line under the appropriate percentage desired. For example, an eight-year old child weighing fifty-seven pounds and measuring 4 feet 2 inches in height would be nearest the ten-year old category. If 50 per cent oxygen were prescribed the flow required (use second line and 50 per cent column) would be 7.5 liters per minute. For patients over fifteen years of age use last three lines in Table II. The suggested oxygen flows shown in the body of Table II will provide the oxygen percentages shown at the top. The carbon dioxide level in the hood will be approximately 1 per cent.

The apparatus is illustrated in the accompanying photographs. (Figs. 1 and 2.) The injector or Meter is attached to the oxygen regulator and connected to the head tent by ⅜ inch bore tubing. The ice rack contains sufficient ice to provide adequate cooling for a three-hour period. Insulated ice racks of larger capacity can be procured. The transparent canopy adds to the comfort of the patient and permits ready observation.

TABLE II

FLOWS OF OXYGEN REQUIRED FOR CONCENTRATIONS BETWEEN 40 AND 100 PER CENT IN CHILDREN AND ADULTS, CALCULATED ON THE HEIGHT-WEIGHT RATIO*

Age	Height	Weight (lb.)	Estimated CO_2 Output	Oxygen Flow in Liters Per Minute							
				40%	45%	50%	60%	70%	80%	90%	100%
5	3'7"	41	156	4.0	5.0	5.5	7.5	9.5	11.5	12.5	15.5
10	4'5"	68	206	5.0	6.5	7.5	10.0	12.5	15.5	18.0	20.5
15	5'5"	123	281	7.0	8.5	10.5	14.0	17.5	21.0	24.5	28.0
Small adult	5'2"	130	231	5.5	7.0	8.5	11.5	14.5	17.0	20.0	23.0
Medium adult	5'7"	148	259	6.5	8.0	9.5	13.0	16.0	19.5	23.0	26.0
Large adult	6'2"	184	308	7.5	9.5	11.5	15.5	19.5	23.0	27.0	31.0

* The table was prepared as follows: The average height, weight and age relationships were obtained from tables prepared by Dr. Bird T. Baldwin and Dr. Thomas Wood. These tables are published by the American Child Health Association. Additional data regarding height and weight was obtained from "Personal Health Standard and Scale" by Dr. Thomas Wood and published by the Bureau of Publications, Teachers College, Columbia University. Values for males were chosen since they were higher for each of the categories shown.

Surface areas and oxygen consumption values (not shown in Table) were calculated from Dubois body surface area and normal standard charts.

The probable carbon dioxide output was calculated from the oxygen consumption values. An RQ of 0.9 and an increase of 25 per cent in the carbon dioxide output above basal conditions was assumed.

FIG. 1. Closed head tent with plastic ice rack and injector (attached to the regulator) for delivery of the prescribed oxygen concentration.

FIG. 2. Infant model of the closed head tent with ice rack and oxygen concentration meter.

The plastic now employed is torn only with great difficulty. Oxygen percentages in the tent reach the level of the percentage settings of the Meter within fifteen minutes after onset of flow of gas.

The prescribed oxygen concentration is maintained in the tent by setting the injector (Meter) between 40 and 100 per cent.

PATIENT	HEIGHT INCHES	WEIGHT POUNDS	CO 2 OUTPUT CC. PER MINUTE
LARGE ADULT	74	184	
MEDIUM ADULT	67	148	
SMALL ADULT	62	130	
CHILD OF 10 YEARS	53	68	
CHILD OF 5 YEARS	43	41	

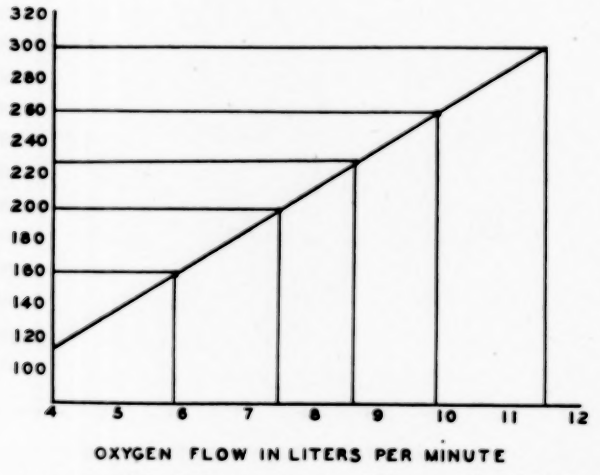


FIG. 3. Oxygen flow requirement to provide 50% oxygen in different sized adults and children.

The oxygen flow requirement to provide 50 per cent oxygen in different sized adults and children is shown in Figure 3.

SUMMARY

A head tent is described in which an injector is used for the purpose of adding a combined oxygen and air atmosphere adequate to wash out carbon dioxide exhaled by the patient.

The apparatus is comfortable, effective and relatively inexpensive.

REFERENCES

1. BURGESS, A. M., BRIGGS, A. S. and BURGESS, A. M., JR. Oxygen therapy by the open box method. *New England J. Med.*, 210: 254, 1934.
2. BURGESS, A. M. Oxygen therapy—a modification of the box method for giving 95 per cent oxygen. *New England J. Med.*, 216: 467, 1937.
3. SAKLAD, M. and BURGESS, A. M. New apparatus for administration of 95 per cent oxygen. *J. A. M. A.*, 124: 831, 1944.
4. BARACH, A. L. and ECKMAN, M. A mask apparatus which provides high oxygen concentrations with accurate control of the percentage of oxygen in the inspired air and without accumulation of carbon dioxide. *J. Aviation Med.*, 12: 39–52, 1941.
5. BARACH, A. L. and ECKMAN, M. A physiologically controlled oxygen mask apparatus. *Anesthesiology*, 2: 421, 1941.

The Effect of Propylene Glycol on the Antibiotic Activity of Human Serum*

SAMUEL J. PRIGAL, M.D., THOMAS H. MCGAVACK, M.D. *and* MARY BELL, B.S.

NEW YORK, NEW YORK

STUDIES with penicillin aerosol, obtained by means of a combined steam generator and aerosolizer,[1,2] disclosed that penicillin, dissolved in propylene glycol 19 parts and glycerine 1 part, produces a stable aerosol. Unusually high "penicillin" blood levels of long duration were obtained by keeping the patient for one hour in a tent into which this penicillin-propylene glycol aerosol was blown, or by making him inhale by means of a tube and mask from a box into which the aerosol was blown and confined.[3] (Table I.) The determination of antibiotic activity in these and all experiments recorded below were made according to the method described by Randall, Price and Welch,[4] which makes use of a certain strain of B. subtilis as the organism for determining penicillin-like activity.

Because of these very high, long sustained values, similar studies were made with propylene glycol and glycerol respectively. These revealed that propylene glycol, when inhaled as an aerosol, imparted antibiotic activity to the blood of patients whose sera were previously inactive. (Table I.) The antibiotic potency of the propylene glycol in vitro before aerosolization was 0.031 units, which is considerably less than the value of 0.5 units repeatedly obtained by inhalation of the aerosol. (Table I.)

Table I also shows that in the aerosols containing penicillin, the antibiotic properties of the blood were not entirely due to the glycol. When the amount of propylene glycol was kept constant, the addition of penicillin invariably increased such antibiotic activity; that is, raised the levels of "penicillin" in the blood.

Propylene glycol was then given to patients orally, intravenously and intramuscularly. The antibiotic activity is recorded in Table II.

TABLE I

"PENICILLIN" BLOOD LEVELS OBTAINED BY INHALATION OF PENICILLIN-PROPYLENE GLYCOL AEROSOL

Method of Confining the Aerosol	Aerosol			"Penicillin" Blood Levels (Units/cc.)						
				Time in Hours						
	Penicillin (Units)	Propylene Glycol (cc.)	Glycerol (cc.)	½	1	2	3	4	5	6
Tent*	100,000	19	1	.25	.25	.25	.25	.125	.125	
	200,000	19	1	.125	1.0	1.0	.5	.5	.5	.5
Breathing Box†	50,000	19	1	1.0	1.0	1.0	1.0	1.0	1.0	.5
	100,000	19	1	1.0	1.0	1.0	1.0	1.0	.5	.5
	200,000	19	1	2.0	2.0	2.0	2.0	2.0	1.5	1.5
	0	19	0	.5	.5	.5	.5	.25	.25	.25
	0	19	0	.5	.5	.5	.5	.5	.5	.5
	0	19	0	.5	.5	.5	.5	.5	.5	.25
	0	0	1	0	.0	0	0	0	0	0

* Patient in the tent for 1 hour.
† Patient inhales from the box for about ½ hour.

It is obvious that propylene glycol, when introduced into the body by pulmonary, intravenous or intramuscular routes, imparts

* From The Department of Medicine, New York Medical College, and the Metropolitan Hospital Research Unit, Welfare Island, New York City. Aided by a grant from Mr. Martin Goodman, New York City.

to the blood some antibiotic activity lasting six hours.

In view of the fact that some normal human sera display natural antibiotic activity against B. subtilis,[5,6] these sera were tested prior to treatment. Two of these sera (from patients M. C. and P. C.) showed initial antibiotic activity equivalent to 0.031 penicillin units per cc. prior to treatment. The actual antibiotic activity due to the presence of propylene glycol in these cases is, therefore, equal to that recorded in Table II minus 0.031 for each reading.

TABLE II
ANTIBIOTIC ACTIVITY OF HUMAN SERUM FOLLOWING ADMINISTRATION OF PROPYLENE GLYCOL ORALLY, INTRAMUSCULARLY AND INTRAVENOUSLY

Propylene Glycol			Antibiotic Activity of Serum (Units/cc.)							
Method of Administration	Amount (cc.)	Patient	Before Treatment	Time in hours						
				½	1	2	3	4	6	8
Oral	10	G.	0	0	0	0	0	0		
	10	B.	0	0	0	0	0	0		
Intramuscular	6	D.	0	.5	.5	.5	.5	.5		
	5	M.C.	0.031	.5	.5	.5	..	.5	.25	0
	5	D.S.	0	.5	.5	.5	..	.5	.5	0
Intravenous	6	R.	0	1.0	1.0	1.0	1.0	1.0		
	5	F.	0	1.0	1.0	1.0	..	1.0	.5	0
	5	P.C.	0.031	1.0	1.0	1.0	..	1.0	1.0	0

Inasmuch as undiluted propylene glycol repeatedly gave an antibacterial value of 0.031 units per cc., the effect of dilution upon its antibiotic activity was tested. Normal human serum, beef broth and water, respectively, were employed as diluents. The results are recorded in Table III.

It seems clear that dilution *per se* is not responsible for the antibiotic activity of the propylene glycol, but that the glycol and serum are jointly responsible. (Table III.)

As further evidence of the antibiotic activity of the propylene glycol-serum mixture, ½ cc. of each of the dilutions with serum from 1 to 10 through 1 to 100,000,000 were incubated for twenty-four hours at 37°C. with 1½ cc. of a suspension of B. subtilis (1–100). No growth occurred in any dilution up to 1 to 10,000,000. Beyond this dilution there was growth. Identical results were obtained in three trials.

TABLE III
ANTIBIOTIC ACTIVITY, IN VITRO, OF DILUTIONS OF PROPYLENE GLYCOL WITH SERUM, WATER AND BROTH

Dilution	Antibiotic Activity (Units/cc.)				
	Serum (4 Determinations)	Water (2 Determinations)	Beef Broth (1 Determination)	Undiluted Propylene Glycol	Undiluted Serum
1–10	0.25	0	0	.031	0
1–100	0.25	0	0		
1–1000	0.25	0	0		
1–10,000	0.25	0	0		
1–100,000	0.25	0	0		
1–1,000,000	0.25	0	0		
1–10,000,000	0.25				
1–100,000,000	0				

When a combined aerosol of penicillin and propylene glycol is administered (Table I), it is possible to estimate quantitatively the antibiotic effect of penicillin and propylene glycol respectively, by the use of penicillinase, which inactivates the penicillin. Thus, a patient was treated with an aerosol of 50,000 units of penicillin dissolved in 19 cc. of propylene glycol and 1 cc. of glycerol. Blood specimens were taken at ½ hour and 1 hour intervals. Half of each of these specimens was treated with penicillinase; the remainder was untreated. Estimation of antibiotic activity of these specimens revealed that the penicillinase-treated sera showed an antibiotic activity of 0.25 penicillin units per cc. (due to the glycol), whereas the untreated sera showed values of 0.5 penicillin units per cc. (expressing the com-

bined antibiotic activity of penicillin and propylene glycol).

Whether the same type of antibiotic effect of the propylene glycol serum mixture is exerted upon organisms other than the one employed in these experiments remains to be seen. Studies along these lines are now in progress.

These observations on the antibiotic activity of a propylene glycol aerosol coincide with the clinical experience of one of us (S. J. P.), who has been treating asthma and allergic rhinitis associated with infection in the respiratory tract with aerosols of penicillin-propylene glycol. For control purposes, some of the patients were treated with propylene glycol aerosol without penicillin and in a few instances favorable results were noted.

COMMENTS

The bactericidal properties of propylene glycol have been investigated by Robertson and his co-workers.[7,8] They observed that whereas the liquid displayed rather low germicidal properties, except in concentrations of 80 per cent to 90 per cent, the aerosol was highly effective in dilutions of 1 Gm. of propylene glycol in two to four million cc. of air. The vapor of propylene glycol was even more effective, 1 Gm. in 10–20,000,000 cc. of air almost instantly sterilizing the atmosphere against a variety of organisms and the virus of influenza.[8] The lethal action of the glycol in vapor form was explained by the high affinity of this glycol for water, with which it is miscible in all proportions. When the vapor contacted an organism, it quickly reached a concentration of 70 to 80 per cent within the cell, and thereby exerted its lethal action.

This does not account for the phenomenon observed when propylene glycol is mixed with normal human serum or plasma. Apparently, a combination of the glycol and some factor in the serum is effected, which results in antibiotic activity of a degree possessed by neither alone.

CONCLUSION

Propylene glycol in serum exerts marked bactericidal properties against a strain of B. subtilis. Such a degree of antibiotic activity (one part glycol to ten million parts serum) is displayed by neither glycol nor serum alone. This antibiotic activity is due possibly to a combination effected by the propylene glycol with some factor in the serum.

REFERENCES

1. Prigal, S. J. and Speer, F. D. A new method of aerosolization of penicillin, sulfonamides, and other medications for inhalation therapy. *Bull. New York M. Coll.*, 8: 21, 1945.
2. Prigal, S. J. The production of aerosols from medicated solutions; a combined steam generator and aerosolizer. *J. A. M. A.*, 131: 398, 1946.
3. Prigal, S. J., McGavack, T. H., Speer, F. D. and Harris, R. Blood levels of penicillin obtained by inhalation of aerosols produced by a combined steam generator and aerosolizer, with the use of propylene glycol, tents and a breathing box. *J. A. M. A.* (to be published).
4. Randall, W. S., Price, C. W. and Welch, H. The determination of penicillin in body fluids. *Science*, 101: 262, 1945.
5. Briggs, C. W., Bronstein, B., Hirshfield, J. W. and Pilling, M. A. The presence in normal serum of inhibiting substances against B. subtilis. *Science*, 103: 363, 1946.
6. Chandler, V. L., Price, C. W. and Randall, W. A. Control and evaluation of blood serum assays for penicillin. *Science*, 102: 255, 1945.
7. Robertson, O. H., Biggs, E., Puck, T. T. and Miller, B. The bactericidal action of propylene glycol vapors on micro-organisms suspended in air. *J. Exper. Med.*, 75: 593, 1943.
8. Robertson, O. H. Sterilization of air with glycol vapors. *Harvey Lectures*, 38: 227, 1943.

Management of Acute Toxic Nephrosis

VICTOR H. KUGEL, M.D.*

MIAMI BEACH, FLORIDA

ACUTE toxic nephrosis is the clinical syndrome produced by a particular type of acute renal injury. Clinically, it is manifested by decreased or absent urinary output, fluid retention, progressive azotemia, plethora, hypertension, cardiac dilatation and pulmonary edema. Variable degrees of albuminuria and abnormal urinary sediment are present, and the low specific gravity of the urine persists throughout and after the acute episode. The dominant pathological feature is acute, selective damage to renal tubular epithelium. The etiological agents are diverse,[1] as many as thirty-four according to Peters,[2] but the more clearly delineated ones are carbon tetrachloride poisoning, hemolytic transfusion reaction and crush syndrome. The mortality rate is high, yet when recovery occurs it is usually complete.[1,3,4]

Confronted with the urgency of the acute disorder, the alternative of death or complete recovery of the patient, and the lack of specific therapy, the physician who seeks aid in the management of the critically ill patient is offered a bewildering variety of therapeutic suggestions. Some of these therapeutic suggestions are diametrically opposed in principle and the efficacy of all of them is disputed.

Since spontaneous recovery occurs, it would seem logical to accept this as a basic principle in the management of acute toxic nephrosis. Thus one may endeavor to determine which therapeutic measures may aid and which may harm spontaneous recovery. This basic concept also affords a standard for the critical evaluation of proposed medical and surgical therapeutic procedures. The following case reports illustrate the feature of spontaneous recovery and indicate some of the problems of management.

CASE REPORTS

CASE 1. *Acute Toxic Nephrosis Due to Carbon Tetrachloride.*[4] This twenty-two year old soldier became acutely ill after two days of intermittent inhalation of carbon tetrachloride used in degreasing guns. Nine of fifteen men similarly exposed to this agent became acutely ill and eight of them recovered fully after forty-eight hours. This patient, however, progressed to renal insufficiency; in this connection, a past history of alcoholism is significant. About five hours after the last exposure to carbon tetrachloride, the patient had nausea, vomiting, dizziness, weakness, backache, pains radiating down the back of the legs, fever and tachycardia. He was hospitalized and received morphine sulphate, atropine sulphate, and repeated intravenous injections of 10 per cent glucose, physiological saline and calcium gluconate. On the third day of illness the symptoms were aggravated, abdominal pain and distention were additional complaints, and attention was directed for the first time to an oliguria. There was no improvement following repeated intravenous infusions. On the fourth day of illness, he was transferred to another hospital where he came under our observation.

Examination disclosed an apathetic, nauseated, drowsy patient with a temperature of 98.2°F., a pulse of 64 and respirations 24. The eyes were puffy, the sclerae subicteric and there was a uriniferous odor to the breath. Slight bleeding from the right nostril, moderate stomatitis, and an ulceration of the right tonsil

*Consultant in Cardiology, Nautilus Hospital (Veterans' Administration), Miami Beach, Fla.

were noted. The heart and lungs were normal. The blood pressure was 140/110. The abdomen was distended, the liver edge palpable one to two finger breadths below the costal border and tender. There was mild costovertebral tenderness. The kidneys were not palpated. The

The daily fluid intake of the first six days of illness ranged from 2,000 cc. to 3,720 cc. (average 2,600 cc.) and from the fourth to the eleventh day fluids were given chiefly intravenously. In addition to infusions of 5 per cent glucose alternately in saline and distilled water,

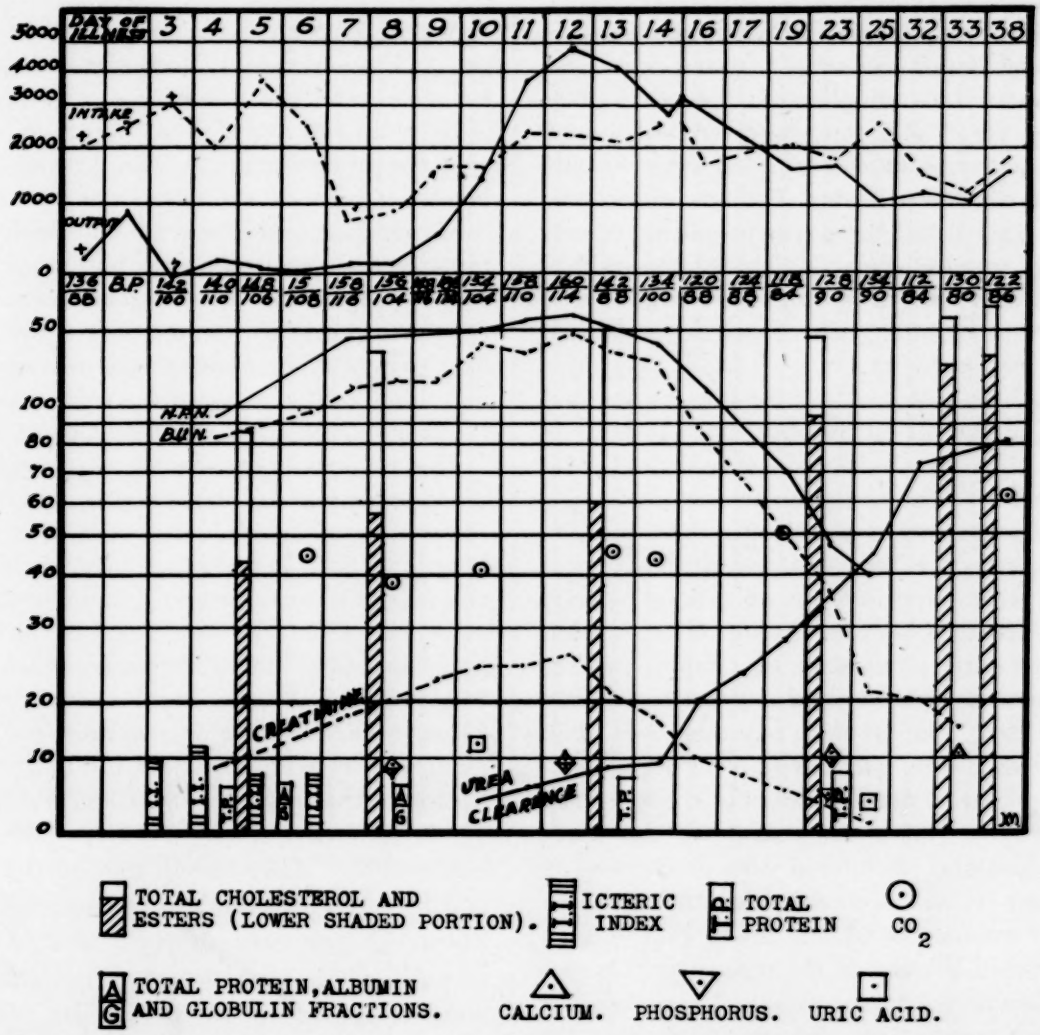


FIG. 1. Composite of intake, output, blood pressure and blood chemistry. Observations charted on semilogarithmic paper. Non-protein nitrogen, blood urea nitrogen, cholesterol and cholesterol esters, creatinine, calcium, phosphorus and uric acid recorded in mg. per cent; icteric index in conventional units; total protein in Gm. per cent; CO_2 in volumes per cent; urea clearance in per cent of average normal function.

history indicated anuria for the preceding twenty-four hours; severe oliguria was present and persisted. Laboratory studies corroborated the clinical impression of predominant renal insufficiency. (Fig. 1.) Details of fluid intake and output, blood pressure, blood chemistry and urea clearances are summarized in Figure 1.

the patient received 50 per cent glucose, 300 cc. of plasma and several injections daily of 10 cc. of 10 per cent calcium gluconate.

On the sixth day there was puffiness of the face and skin but no pitting edema. On the seventh day, the patient's condition appeared critical. Headache was a prominent complaint,

nausea and vomiting increased and he vomited a total of 180 cc. of frankly bloody material. A superficial scratch of the neck resulted in profuse bleeding that required compression. Epistaxis was another manifestation of this bleeding tendency that apparently responded to vitamin K since the bleeding tendency disappeared after forty-eight hours of administration of this vitamin. The pulmonic second sound was now accentuated and reduplicated; the blood pressure was 158/116. There was severe abdominal pain. The liver edge was enlarged to the umbilicus and markedly tender. Puffiness of the skin had increased, but there was no pitting edema and the lungs were clear. The blood non-protein nitrogen had risen to 146 mg. per cent, the urea nitrogen to 110 mg. per cent and the creatinine was 18 mg. per cent.

On this seventh day of illness it was decided to discontinue all intravenous fluids and allow the patient only a minimum of oral fluid. The patient felt better on the eighth day, although crackling râles were noted in the chest and pitting peripheral edema was present. There was cough with expectoration of thick, bloody, muco-purulent sputum. *X*-ray of the chest disclosed early pulmonary congestion, patches of bronchopneumonia and borderline cardiac enlargement. On the ninth day there was frank congestive failure, with numerous rales at both bases, probable ascites, markedly enlarged and tender liver, and pitting edema of the lower extremities and abdominal wall. A chest *x*-ray exhibited remarkable cardiac enlargement, increased pulmonary edema, bronchopneumonia and a small effusion at the right base. On this day there also occurred an alarming episode of forty-five minutes' duration in which there was confusion, severe headache, mild convulsions, progressive impairment of vision including transient blindness, and abrupt elevation of the blood pressure to 186 systolic and 124 diastolic.

The precarious state was still present on the tenth day. However, for the first time, the output approached the fluid intake. From the eleventh through the eighteenth day there was a striking diuresis of nearly twenty-six liters. With the onset of diuresis there was immediate and striking clinical improvement, the symptoms disappeared rapidly, the appetite returned promptly, and clinical evidences of water retention disappeared within forty-eight hours. *X*-ray of the chest on the sixteenth day revealed the heart and lungs to be normal. A notable tissue weight loss was restored to normal within several weeks.

Improvement in the laboratory findings was not as spectacular. Actually, the maximum figures of nitrogen retention (non-protein nitrogen 173 mg. per cent, urea nitrogen 148 mg. per cent, and creatinine 26.4 mg. per cent) were obtained more than twenty-four hours after the onset of diuresis. The azotemia diminished relatively slowly and it was not until the twenty-fifth day of illness that the non-protein nitrogen and creatinine were normal, while the urea nitrogen did not become normal until the thirty-third day. On the thirty-third day the urea clearance was about 80 per cent of average normal, but the maximum specific gravity in the concentration test was only 1.020.

The clinical improvement that began with the diuresis continued rapidly to the complete restoration of health. After forty-five days of hospitalization, including a furlough, the patient was able to return to unlimited duty. All evidences of hepatic, renal and cardiac damage had disappeared, the blood pressure ranged from 112/84 to 130/80, the urea clearance test was 89 per cent of average normal function, and the maximum specific gravity of the urine concentration test was 1.024. (Fig. 1 and Table 1.)

Comment. This case illustrates the typical acute renal insufficiency that occurs in about 23 per cent of the cases of carbon tetrachloride poisoning.[5] The inhalation route of poisoning and alcoholism predispose to the development of this renal lesion.[4,5] Although acute toxic manifestations, including gastrointestinal irritation and mild hepatic damage, were the initial presenting features, the acute toxic nephrosis predominated after forty-eight hours of illness. Oliguria and anuria were followed by fluid retention, hypertension, azotemia, edema and anasarca of renal, subsequently of cardiac and renal origins, rapid cardiac dilatation and decompensation, pulmonary

TABLE I

URINARY FINDINGS

Case I

Day of Illness	1	2	3	4	5	6	7	8	9	11	13	16	24	29	33	38	48	57	120
Urine																			
Sp. Gr.			QNS	QNS	QNS		1.007	1.008	1.009		1.009	1.012	1.018*		1.020*	1.024			
Albumin			4+	2+	3+		2+	1+	2+		0	0				0			
Epithclial cells				15					Few							Few			
WBC			10–15	10	Num.		Num.	15–20	Occ.		4–6	30–35			4–6	10–12			
RBC							6–8	12–15	Num.		15–20		0		0	0			
Casts				1	1		3		2				0		0	0			

Case II

Urine																			
Sp. Gr.	1.018‡	1.015†	1.012		QNS		QNS	1.014	QNS	1.009	1.006	1.005	1.005	1.008	1.013*		1.018	1.018*	1.018*	1.030*
Color	Straw	Dark Amber	Dark Amber		Dark Brown		Dark Brn	Light Brown	Dark Straw	Straw	Straw	Straw	Straw	Straw						
Reaction	5.5		5.0		6.5		6.5	6.5	6.5	7.0	6.5	6.5	5.0	6.5	5.5					
Albumin	0	2+	3+		4+		4+	4+	3+	3+	1+	1+	1+	0						
Epith. cells	0	Many	Many																	
WBC	0	Few	Few		Many		2+	1+		Occ.	2+	10–15	15–20	Occ.						
RBC	0	Many	Few		Many		2+	1+	6–8	7–8	15–25	3+	Plus	Occ.						
Casts	0	Occ.	Occ.		Occ.			0				Occ.								
Sediment	0	Much	Hem. crystals		Much		2+	2+		0	0									

* Specific gravity, where underlined, indicates maximum specific gravity of concentration test. Sediment is charted either qualitatively or in units per high power field of centrifuged specimen.

† Specimen voided immediately after transfusion reaction.

‡ Preoperative specimen.

edema, hypertensive encephalopathy and bronchopneumonia.

Fluids were forced moderately for the first six days, averaging 2,600 cc. daily. From the fourth day, fluids were given chiefly by intravenous route and vomiting diminished. Oliguria, however, persisted and the patient's critical state and dubious prognosis evoked a conference on therapy on the seventh day. Numerous therapeutic procedures were discussed and serious consideration was given to (1) more vigorous administration of fluid, (2) hypertonic fluids, (3) diuretics, (4) lavage of renal pelvis, (5) decapsulation of kidneys and (6) sympathetic nerve block. Fortunately, none of these procedures was employed; the minority recommendation of fluid restriction was adopted. Fluid restriction at this stage, however, did not prevent cardiac dilatation, anasarca, pulmonary edema, and hypertensive encephalopathy that ensued after another forty-eight hours of oliguria; it did, undoubtedly, contribute to the eventual recovery.

The urinary output increased slightly on the ninth day, exceeded 1,000 cc. on the tenth day, and a striking, spontaneous diuresis of 26 liters occurred in the subsequent week. As soon as diuresis began, the clinical picture changed promptly, in a manner approaching a crisis. The abatement of the azotemia was not parallel. (Fig. 1.) On the sixteenth day the patient was virtually asymptomatic. He enjoyed a diet of 2,500 calories composed of 450 Gm. of carbohydrate, 50 Gm. of protein and 20 Gm. of fat. There was no evidence of water retention, no cardiac abnormality, and his blood pressure was 120/88, yet the elevation of non-protein nitrogen, urea nitrogen and creatinine was of the same magnitude as on the fourth day of illness.

There were other indications of damaged tubular epithelium aside from the slow excretion of nitrogenous products. In the oliguric, prediuretic phase, the urine specific gravity was constantly low, ranging from 1.007 to 1.009. The maximum urine specific gravity in the diuretic period increased to 1.014. The maximum specific gravity of the urine concentration test increased only slowly in the post-diuretic period: 1.018 on the twenty-fourth day, 1.020 on the thirty-third day, and 1.024 on the thirty-eighth day. The return of the ability to excrete water was not accompanied by an equivalent ability to excrete and concentrate solutes. This was also demonstrated by the urea clearance test; on the tenth day (prediuresis) it was 4 per cent of average normal and, in the subsequent three weeks, there was a slow, linear return to normal values.

Clinical recovery was complete when the patient was last seen on the forty-fifth day of observation. Laboratory indications of renal involvement were likewise absent save for the mild diminution in maximum urine concentration.

CASE II. *Acute Toxic Nephrosis from Hemolytic Transfusion Reaction* ("*Transfusion Kidney*"). This twenty-nine-year old soldier suffered a penetrating wound of the left leg and a severe compound comminuted fracture of the left tibia during action in November, 1944. Four months later, when he arrived in the Zone of Interior, he was still bedridden and chronically ill from an active, secondary osteomyelitis. The cardiovascular and renal systems were normal; the blood pressure averaged 136/80. The past history was non-contributory.

On March 27, 1945, he underwent a saucerization of the left tibia. A transfusion was given postoperatively to promote healing. Shortly after he had already received about 135 cc. of blood, the patient felt uneasy, complained of severe backache, vomited a watery, sanguineous fluid and had a shaking chill. The transfusion was promptly discontinued and the patient felt better. An hour later, however, there was a profuse hemorrhage through the leg cast (estimated loss of 750–1,000 cc.). Shock developed, the blood pressure fell to 70/30, and

he voided a grossly bloody urine. Although the shock state responded to therapy that included intravenous fluids, plasma and sodium bicarbonate, the patient became anuric and was transferred to the Cardiovascular-renal Section for treatment. Subsequent studies disclosed this to be an incompatible transfusion reaction; a recheck of the cross-matching revealed the donor to be in Group A (weak agglutinogens) and not in Group O as previously typed by two laboratories. The patient was in Group O.

Figure 2 summarizes the pertinent features of the fluid intake and output, blood, blood pressure and blood chemistry studies. After the initial use of parenteral fluids to combat shock and to stimulate diuresis, fluids were restricted to an intake of 650–1,350 cc. daily. Included in this intake total are indirect transfusions of whole blood, preceded by 10 cc. of 10 per cent calcium gluconate, on the second, third and fourth days. Not included in the intake is the very thick oatmeal gruel given from the fourth day on in amounts of not over 200 cc. daily. Oral fluid intake was minimal until the fourth day. Thereafter, the patient was encouraged to take an ounce of thick gruel every hour. The vomiting diminished despite the progressive renal insufficiency and the patient was happier. Because of this oral tolerance and the aggravation of vomiting by intravenous fluids, particularly by 50 per cent glucose, all parenteral fluids were discontinued after the seventh day. With the onset of diuresis, the chief guide to oral fluid intake was the patient's thirst.

The post-transfusion course was generally afebrile except for an occasional rise to 101°F. Headache, cough, mild hiccough, costovertebral tenderness, nausea and vomiting were the earliest symptoms; the latter persisted into the period of diuresis. Following the hemolytic transfusion reaction the patient voided about 300 cc., then became anuric for thirty-six hours; an output of 210 cc. (pH 5.5) was again followed by forty hours of anuria, in turn followed by severe oliguria. Urinary output increased progressively on the ninth, tenth and eleventh days until diuresis appeared from the twelfth to the twentieth day.

Neck vein distention, labored breathing, and abdominal distention appeared on the third day of illness. The liver edge was palpable at two fingerbreadths on the fifth day and reached a maximum of four fingerbreadths on the eighth day. Hypertension was noted on the seventh day and was maximum (160/112) on the eighth day. On this day there were indications of significant fluid retention and early cardiovascular embarrassment. The patient was dyspneic on slight exertion, his face was puffy, there were scattered, crackling rales at the bases of the lungs, the heart action was forceful, P_2 was accentuated, the apical first sound was thumping, a faint apical systolic murmur was noted, the liver was enlarged to four fingerbreadths, and a portable x-ray of the chest disclosed accentuated bronchovascular markings and a delineation of the right interlobar septum.

Between the ninth and eleventh days the general condition was stationary, but with the onset of diuresis on the twelfth day there was prompt and striking improvement despite the azotemia that reached its peak on the thirteenth day (non-protein nitrogen 172 mg. per cent, urea nitrogen 150 mg. per cent) and then declined over a period of eight days. After twenty-four hours of diuresis, P_2 was no longer accentuated, the pulse was not bounding, the blood pressure fell to 146/96, the liver decreased in size, and the patient enjoyed a 1,200 calorie diet. Improvement was rapid and progressive thereafter, the hypertension disappeared after the sixteenth day, and a chest film disclosed diminution of the bronchovascular shadows and disappearance of the previously delineated interlobar septum. On completion of diuresis the extremities were notably thin, shrunken and the skin was wrinkled, indicative not only of marked fluid retention but also of a significant loss of tissue substance.

Improvement in renal function was slower, the urea nitrogen being still elevated after completion of diuresis. A normal urine concentration test (Table 1) was not obtained on the fifty-seventh day and the urea clearance test was still subnormal on the fifty-fourth day. Follow-up studies four months after the hemolytic reaction revealed complete clinical and laboratory cure. Eleven months after the acute toxic nephrosis the patient was re-examined and no abnormalities were detected in the renal or

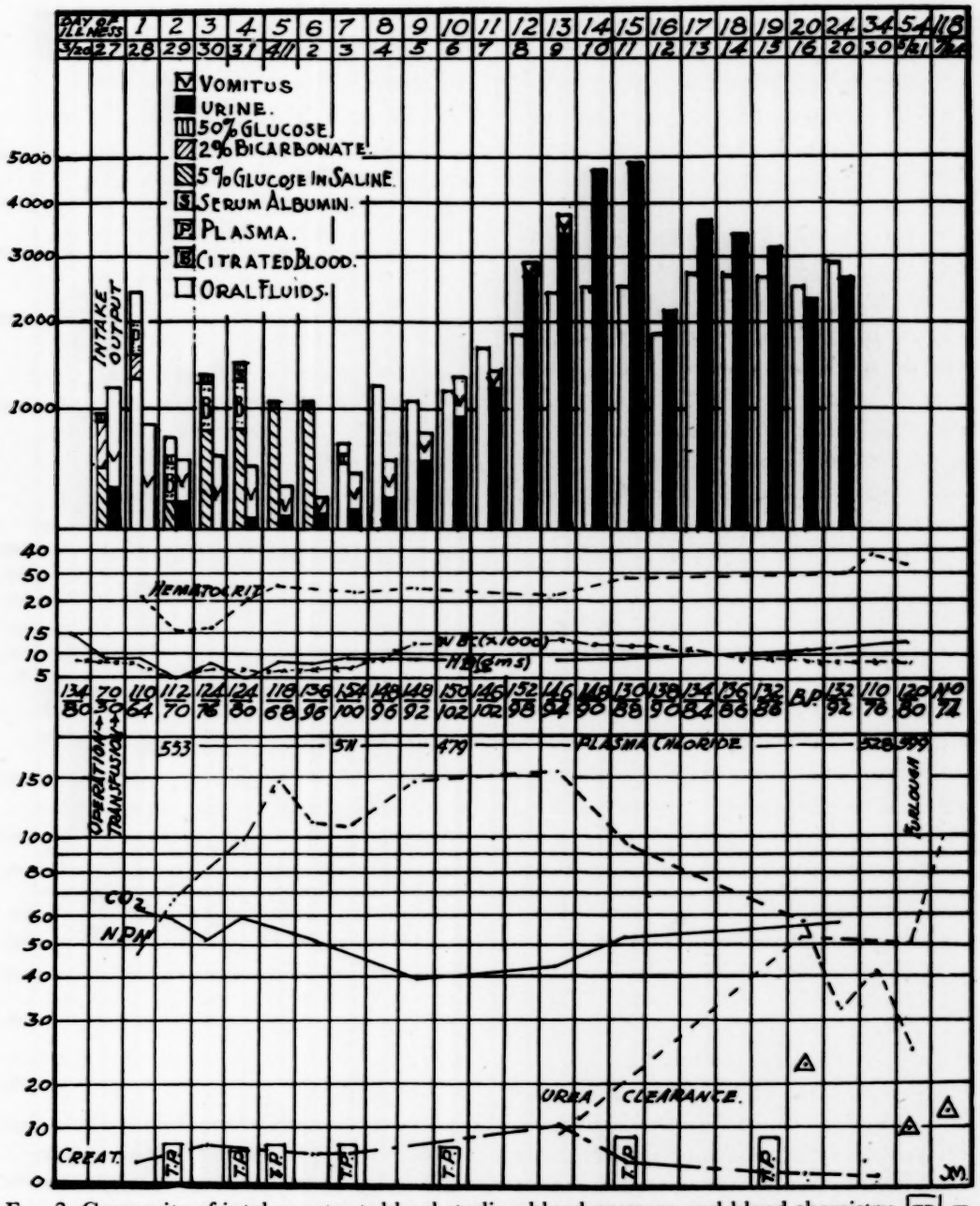


FIG. 2. Composite of intake, output, blood studies, blood pressure and blood chemistry. [TP] = Total protein. ▽ = Blood urea nitrogen. Intake, output and blood chemistry charted on semi-logarithmic paper. Chlorides, non-protein nitrogen, blood urea nitrogen and creatinine recorded in mg. per cent; CO_2 in volumes per cent; total proteins in Gm. per cent; urea clearance in per cent of average normal function.

cardiac systems by clinical and laboratory studies.

Comment. This is also a typical example of acute toxic nephrosis, in this instance resulting from an incompatible transfusion reaction. Judged by the amount of incompatible blood administered, the prognosis was relatively favorable.[6] Judged by the degree and duration of oliguria and anuria, nitrogen retention and other clinical and laboratory abnormalities, the degree of renal insufficiency was indistinguishable from reported cases with fatal termination. Severe hemorrhage and shock were additional hazardous complications. Transfusions, employed gingerly at first and more boldly later, corrected the complicating anemia but had no immediate effect on restoring renal function. Anuria and oliguria were followed by progressive azotemia, fluid retention, plethora, hepatomegaly, hypertension, cardiovascular embarrassment, and latent pulmonary edema.

After the initial use of parenteral fluids and plasma succeeded in combatting shock, but failed to maintain adequate urinary output, fluid intake was restricted. A fixed daily intake was not prescribed, but enough fluids were given to equal approximately the estimated insensible fluid loss plus that amount lost by vomiting. As occurred with Case 1, the disquieting status of the patient at the end of a week evoked a conference on therapy. No two internists or surgeons could agree on a plan for future therapy, but there was general disapproval of the unorthodox restriction of fluids and avoidance of parenteral therapy. A variety of medical and surgical procedures were individually championed. No actual change in the management was made, however, and spontaneous recovery fortunately ensued.

Calculation of the gross intake and output (Fig. 2) for the first nineteen days discloses an excess of output over intake of about 1,400 cc. At first glance, this discrepancy might be dismissed as within the limits of error. When, however, there is included in the output the insensible loss of fluid by lung, skin and bowel (say only 250–500 cc. daily) the excess of output over intake is about 7,500–11,000 cc. Comparable figures are not available for Case 1 but the clinical impression in both cases was that the degree of water retention and diuresis exceeded that expected from the intake. Is there an internal source of this fluid and what is its significance? In both cases, although the exact weight loss is unknown, it was clinically evident at the completion of diuresis that significant weight loss, easily fifteen to twenty-five pounds, had occurred as a result of intoxication, starvation, vomiting, acidosis and fever. Destruction of this amount of tissue will liberate 5,000–10,000 cc. of intracellular fluid. Since water excretion is a fundamental impairment in acute toxic nephrosis, an occult, unsuspected fluid retention thus develops that materially aggravates the edema tendency and its complications. This endogenous source of fluid retention may account for reports of fatal heart failure and pulmonary edema developing in acute toxic nephrosis despite cautious administration of fluids.[7]

Theoretically, potassium intoxication is a possible consequence of this toxic destruction of tissue and liberation of intracellular fluids. Potassium studies were not obtained in the above two cases but there are reports of elevated potassium in crush syndrome.[8] The elevated blood potassium in crush syndrome has been attributed to tissue breakdown in the crushed limb. In animals made anuric by ligation of the ureters or by nephrectomy, potassium poisoning is the cause of death by producing cardiac irregularity and sudden cardiac arrest.[8]

COMMENT

The close similarity in the clinical manifestations, clinical course, and laboratory

findings establish acute toxic nephrosis, of varied etiology, as a clinical syndrome. Figures 1 and 2 resemble not only each other but also other reported cases. These charts also reveal marked similarities in the duration of the oliguria-anuria and pre-diuretic phases, the onset of diuresis on the eleventh and twelfth days, the duration of the diuresis, the hypertension, the degree of azotemia and its relatively slow decline, the reduction of CO_2 combining power, the evidences of impaired tubular function, and the gradual, progressive restoration of tubular function. The urinary findings are also similar (Table 1), although pigment derivatives of hemoglobin (myohemoglobin in crush syndrome) are present in "transfusion kidney" but not in carbon tetrachloride nephrosis.

The similarity in the pathology of this syndrome, especially the selective tubular damage, is evident in the following quotations:

Carbon Tetrachloride. "The anatomic basis for the clinical and renal symptoms is nephrosis characterized by distention of the spaces of Bowman with albuminous precipitate, with swelling of the lining cells, swelling and vacuolation of the cells of the proximal convoluted tubules, degeneration and necrosis of the cells of the distal convoluted tubules and those of the loops of Henle, with desquamation, and by the presence of granular, hyaline and cellular casts in the tubules, with plugging of their lumens. Concretions are present whose nature and significance are obscure."[5]

Hemolytic Transfusion Reaction. "The most characteristic postmortem findings in the patient who died as a result of transfusion of incompatible blood are seen in the kidneys. They are usually somewhat swollen, but otherwise present no pathognomonic gross lesions. Microscopically, the most striking change consists in the presence, within the renal tubules, of pigmented casts, consisting of hemoglobin or the degradation products of hemoglobin. Characteristically, these casts occur only in certain portions of the tubules, namely, the ascending loops of Henle, the distal convoluted tubules and the collecting tubules. Furthermore, the casts are not diffusely but irregularly distributed, and the majority of the tubules may not be involved. Less conspicuous, but perhaps more important, are degenerative or even necrotic changes in the tubular epithelium of relatively short segments of the ascending loops of Henle and the distal tubules. In the neighborhood of the more severely damaged segments, the interstitial tissue often exhibits an inflammatory reaction with small cells predominating. The changes in the tubules and their supporting stroma are usually most evident in the zone between the cortex and the medulla. In contrast to damage affecting the lower portion of the nephron, the upper portion, that is, the glomeruli and the proximal tubules, are usually normal."[9]

Crush Syndrome. "There is no significant change in the glomerular capillaries. The capsular space and the lumen of the first convoluted tubules contain a variable but sometimes considerable amount of amorphous and granular debris . . . The most striking changes are found in the ascending loop of Henle and the second convoluted tubule . . . The epithelium lining this part of a considerable number of nephrons shows clear evidence of necrosis. This change is particularly intense in microscopic foci usually situated in the boundary zone. In these foci the tubular wall is weakened and occasionally ruptured and there are areas of tubular collapse with early fibroblastic and histiocytic proliferation in the interstitial tissue. Epithelial regeneration in this part of the nephron (second convoluted tubule, boundary zone) is clearly present in most cases surviving the seventh day . . . It is in this part of the nephron and in the collecting tubules that the "pigment casts" (myohemoglobin or a simple derivative) so

typical of the condition are seen. In the majority of cases these casts are numerous and conspicuous and become larger and longer as the collecting tubule is reached. In some cases they are relatively scanty."[8]

Analogous experimental changes, that is, severe selective tubular damage to ascending loops of Henle and the second tubules are seen in the poisoning produced by lithium monourate (rabbit),[10] phosphate nephritis of rats,[10] and carbon tetrachloride poisoning in cats.[11]

The studies of the pathology of human acute toxic nephrosis have a common failing in that the specimens are obtained at a stage of fluid retention, as a result not only of oliguria-anuria but also at a stage when oliguria has persisted "in spite of the administration of large volumes of fluid." May not the kidney engorgement, in part at least, reflect the retained fluids and increased blood volume that are responsible for an analogous enlargement of the liver? Solution of this and similar questions is of practical importance since therapy has been predicated on the findings at autopsy.

The pathology of acute toxic nephrosis likewise fails to uncover the pathogenesis of this syndrome. Is the acute renal insufficiency the result of vasoconstriction, edema, tubular blockage, tubular necrosis, nephrotoxic effect, a combination of these effects, or is the cause perhaps still unknown? Is the mechanism that initiates this anuria the same as the sustaining mechanism? How does recovery take place? These are questions of therapeutic importance, for the obstructive theory of acute toxic nephrosis has led to intravenous injections of large amounts of fluid and alkali; the edema theory, to late decapsulation; and the theory of increased intrarenal pressure[2] to immediate decapsulation as an emergency surgical procedure of the same urgency as appendectomy.

The obstructive theory (blockage of renal tubules) is being generally abandoned.[2,6,8,6,10,12] Bywaters[13] pointed out that if the anuria of crush syndrome were due to tubular blockage, any urine secreted must be derived from unobstructed tubules and should be normal; actually, the urine in his cases was little more than a glomerular filtrate. Dunn[10] compared the concentration of urea in blood and urine in crush syndrome and found extreme impairment of concentration power, indicative of severe tubular damage. Cases I and II, as indicated previously, revealed severe tubular damage in both the pre- and postdiuretic phase. Awareness of the pathology of the allied carbon tetrachloride nephrosis might have prevented the therapeutic emphasis on blockage of tubules by hemoglobin and its derivatives by the students of 'transfusion kidney.' Therefore, the theoretical indications for "flushing" the kidneys to overcome a block, using large amounts of fluids, are no longer tenable.

Bilateral renal decapsulation, to relieve "acute congestion and swelling of the kidneys," has fallen into disfavor. Unilateral renal decapsulation still has its advocates.[14,15] Figure 3 was prepared from the material available in articles recommending unilateral decapsulation. Comparison of the urinary output in Figures 1, 2 and 3 reveals a very similar course. It also reveals that decapsulation was performed in the prediuretic period and that there was an appreciable delay between decapsulation and the diuresis. The patients represented in Figure 3 were also treated with daily intravenous infusions of 3,000 or more cc. for prolonged periods.

Johan T. Peters[2] proposes that "the primary cause of the oliguria or anuria is a decrease of the effective filtration pressure as a result of an increased intrarenal pressure." This increased intrarenal pressure may result from dilatation of tubules, interstitial edema, inflammatory exudate and swelling of the

tubular cells. Employing an ingenious mechanical device ("artificial nephron") that imitates the pressure relationships and fluid output of the kidney, Peters finds that an increase of a few millimeters of mercury in the intrarenal pressure may cause

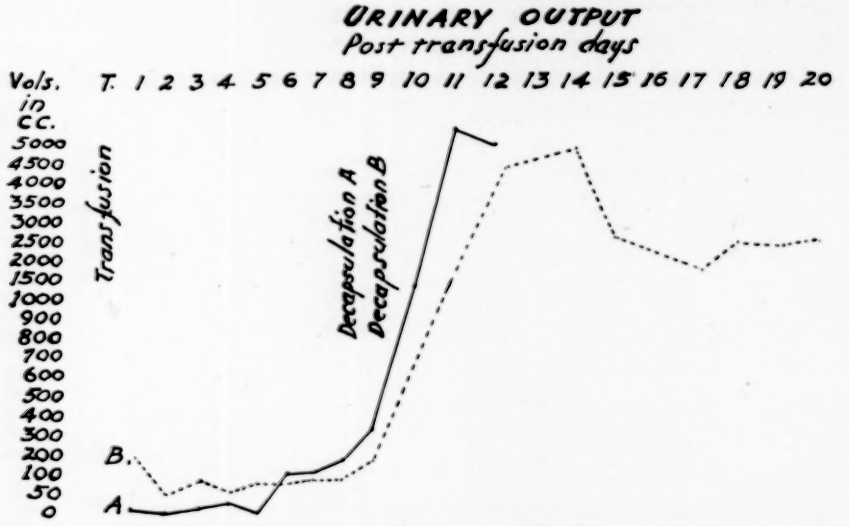


FIG. 3. Data modeled after reports of two cases[14,15] of "successful" unilateral decapsulation.

"oliguria" or "anuria," whereas a slight decrease of an increased intrarenal pressure (analogous to decapsulation *in vivo*) promptly restores the normal "urinary output." From these and other considerations, Peters concludes that "emergency decapsulation in severe cases associated with the syndrome is more urgent than appendectomy in acute appendicitis." The factor of increased intrarenal pressure deserves careful consideration; the therapeutic principle derived from this theory can, and should be, tested in animals rendered acutely nephrotic by carbon tetrachloride, incompatible transfusion, or crushing of an extremity.

There are several objections to the theory of increased intrarenal pressure as the sole or main factor in acute toxic nephrosis. There is no evidence that swelling of the kidneys precedes the initial oliguria. Cases are reported in which the kidney lesion is insignificant.[16] The objections to the interpretation of the swelling of the kidneys noted on autopsy or decapsulation have been previously stated. A more serious criticism is that the intrarenal pressure theory fails to explain the spontaneous diuresis that occurs on the eleventh or twelfth day of illness at a time when fluid retention in the skin, liver, lungs and kidneys is maximum. The theory of increased intrarenal pressure would logically infer that diuresis is least possible at the height of renal swelling.

Discovery of the mechanism of spontaneous diuresis might result in specific therapeutic measures. A relationship worthy of consideration is the aspect of tubular regeneration. In acute toxic nephrosis the basement membrane is usually intact and tubular regeneration is rapid, being first noted on the third day after injury and resulting in complete reclothing of the tubules by epithelium by the fourteenth day.[8] The time relationship of this regeneration to diuresis is suggestive, as is the manner of recovery of tubular function. Were this the mechanism, treatment and prognosis would be concerned with tubular regeneration and the ability to tide the patient over until regeneration has occurred.

With this background of clinical observations, pathology, pathogenesis, and re-

covery mechanisms, it is clear that specific therapy is not now available. Since clinical recovery is initiated by diuresis (although anatomical damage and impaired tubular function persist for an appreciable time thereafter), any measure that would produce diuresis would be a satisfactory therapy. Although a variety of measures have been reported successful in isolated cases, critical evaluation fails to disclose any known successful therapy in a significant number of cases.[6,9] These measures include isotonic or hypertonic fluids ranging from "adequate" to "massive," intravenous sodium bicarbonate or $\frac{1}{6}$ molar sodium lactate, intravenous sodium sulfate, transfusion of compatible blood and plasma, phlebotomy, decapsulation of kidney, irrigation of renal pelves, spinal anesthesia, splanchnic block, diathermy to kidney regions, *x*-ray irradiation of kidney regions and aceytlbetamethylcholine.

Since there is no specific therapy and no reliable method of initiating diuresis, attention is focussed on measures to aid spontaneous recovery. This approach is aided by analyzing the causes of death in acute toxic nephrosis. Of course, in some of the cases, the exposure to the intoxicant is so great and the damage to various organs is so widespread that the downhill course is rapid and relentless due to generalized toxic effects rather than to isolated renal insufficiency. When, however, the acute injury is survived and the course is that of protracted renal insufficiency for seven to ten days, death is commonly reported as "of uremia." The observations and comments in Cases I and II indicate that the degree and duration of the azotemia are not the prime determinants of the illness. Death from transfusion kidney, in four to ten days,[9] and from the crush syndrome, seven days on the average,[8] occurs too soon to be primarily "uremic." A review of unselected fatal cases reveals some interesting observations. (Table II.) Death occurred between the third and thirteenth day, 7.7 days on the average. Although the authors were not particularly concerned with water metabolism and cardiovascular complications, there are clinical and pathological evidences of such effects in nine of the cases. In one instance,[17] (Case I) generalized edema appeared on the second day after the transfusion reaction despite an intake of 2,000 cc. daily. In another patient (Case IV) generalized edema was present on the third day after the reaction and death from pulmonary edema occurred on the following day when the maximum NPN was 112 mg. per cent. One death occurred on the third day; although oliguria was present, the presumptive cause of death in this case was overwhelming intoxication.

These observations from the literature coincide with the observations in the two reported cases that water retention, circulatory overload, cardiac embarrassment and pulmonary edema weigh heavily in the outcome. The puffy appearance, neck vein distention, early onset and progression of liver enlargement, and accentuated pulmonic second sound are clinical manifestations of the embarrassing plethora; recent investigations disclose a circulating blood volume "far above the values for normal" in transfusion anuria.[9] The endogenous source of fluid retention plays a significant and hitherto unappreciated rôle in this train of events. The similarities of the two case reports have been commented on previously; there is one important difference. Case I, on a daily intake of about 2,600 cc. for six days, developed anasarca, cardiac dilatation, congestive failure and pulmonary edema despite restriction of fluids after the sixth day. His recovery despite these complications is a tribute to his youth and sturdy cardiovascular system. (These attributes cannot be predicated in other cases.) Case II, on the contrary, did not progress to congestive failure and pulmonary edema but, even

on an average fluid intake of 1,000 cc. daily, did develop generalized edema, hepatomegaly, probable early cardiac dilatation, cardiac embarrassment, and latent pulmonary edema. In this bedridden, wounded, chronically ill patient the additional burden of cardiac and pulmonary complications probably would not have been tolerated. The early appearance of generalized edema and plethora would indicate an excess of available fluid and would argue against further administration of fluid. Furthermore, excess fluids adversely affect the concentration of electrolytes in the extracellular fluid.[19] Restriction of fluids does not interfere with spontaneous diuresis when the recovery mechanism becomes effective. (Cases I and II.)

A final consideration bearing on the employment of fluids, salts and alkali in acute toxic nephrosis is the appreciation of the role of the kidney in the regulation of water balance, blood volume, electrolytes and acid-base equilibrium. Tubular function, by virtue of absorption and secretion, plays a predominant rôle in this regulatory mechanism. The value of fluids, salt and alkali in toxemia and acidosis is not denied, provided kidney function is adequate. When, however, this regulating function is severely impaired or lost, as results from the marked tubular dysfunction of acute toxic nephrosis, the effects of fluids, salt or alkali are completely unpredictable and potentially harmful. If, as is commonly proposed for hemolytic transfusion reaction, twelve to

TABLE II

DATA RELATING TO DATE AND CAUSE OF DEATH IN 13 UNSELECTED CASES OF ACUTE TOXIC NEPHROSIS

Etiology		Fluids	Clinical Manifestations	Day of Death	Autopsy
Carbon Tetrachloride					
Perry[18]	Case I.	?	Marked congestive failure	10th	Pleural effusion. Marked pulmonary congestion
	Case II.	?	Exaggerated heart sounds Soft tissue edema	5th	Intense congestion of lungs. Extensive hepatic damage
Smetana[5]	Case I.	"Large infusions"	Ascites	10th	Ascites
	Case III.	?	Heart enlarged to left and right Gallop rhythm—No peripheral edema, rapid pulmonary edema	8th	Marked edema of lungs
Hemolytic Reaction					
Daniels[17]	Case I.	2,000 cc. daily	Generalized edema after 48 hrs.	5th	Congestion and edema of lungs
	Case II.	3,000–3,700 cc. daily	Generalized edema	8th	"Considerable" congestion of lungs
	Case III.	"Large amounts"	Generalized edema "Death with pulmonary edema"	13th	Autopsy limited to abdomen
	Case IV.	"Massive quantities"	Generalized edema after 72 hrs	5th	Edematous lungs
	Case X.	Large amounts of fluid and alkali	Maximum NPN 85 mg.%	3rd	No autopsy
	Case XI.	?	?	9th	No autopsy
	Case XII.	3,000 cc. daily	Râles at bases 2nd–3rd day	6th	No autopsy
Crush Syndrome					
Dunn[10]	Case I.	510–3,630 cc. daily (av. 2,000)	Gross edema both legs and chest wall (?trauma)	9th	1,500 cc fluid in each pleural cavity; both lungs edematous
	Case II.	?	?	7th	Slight dilatation right heart

fifteen Gm. of sodium bicarbonate are routinely administered daily, it is uncertain whether there will be any change in the CO_2 combining power or whether alkalosis will ensue. The effects of the sodium ion component of the alkali will certainly result in aggravation of water retention and edema. It is, therefore, proposed: Do not treat the blood chemistry. Restoration of tubular function will, of itself, correct hypochloremia, acidosis and increased blood volume. (Cases I and II.) In an occasional case the depression of chlorides and CO_2 combining power may reach levels that are hazardous *per se;* in such occasional instances, the cautious administration of salt and alkali may be ventured under constant clinical and chemical guidance.

This detailed consideration of the problem of fluid management in acute toxic nephrosis is necessitated by the almost universal acceptance in practice of the advice in text books and articles to treat such patients with fluids, usually intravenously. The amount of fluids recommended ranges from "large volumes" to "adequate." It is not uncommon to find in the same article a recommendation that fluids be "forced" and that pulmonary edema be guarded against. One plan of treatment of post-hemolytic transfusion reaction[20] that recently has been widely circulated recommends: "For prophylaxis . . . if sodium bicarbonate solution is used by mouth or vein, 1,500 cc. of isotonic (one-sixth molar) sodium bicarbonate solution should be given daily in divided doses. If sodium lactate solution (one-sixth molar) is used, the dosages are identical. For therapeutic use with already developed anuria, these dosages may not be sufficient and can be safely tripled the first day and thereafter reduced to the prophylactic dose. Other fluid should be given in addition to the alkaline solution, and in general for every unit of bicarbonate or lactate solution given, an equal quantity of isotonic solution of sodium chloride may be administered." Interpreted literally, this means that the anuric patient may safely receive 4,500 cc. of alkaline solution and 4,500 cc. of isotonic sodium chloride solution on the first day and 1,500 cc. of each solution daily thereafter. That even half this amount is not safe is gaining recent recognition. For example: "Abundant evidence has appeared that not infrequently patients with injury of kidney tubules are harmed rather than helped by persistent efforts to secure diuresis by maintenance of fluid intake in excess of fluid output . . . pulmonary edema is an important cause of death (in hemolytic transfusion reaction*). Thereafter (i.e., after the first twenty-four hours in which an excess of 3,000 cc. is allowed over intake*) fluids are given strictly in accordance with demands of fluid loss."[21]

Even when the dangers of excessive fluid and salt are well recognized and the "greatest stress" is placed on proper regulation of salt and fluid, there is reluctance to accept the logical conclusion: "The oliguric patients (from transfusion reaction*) very often show an increased plasma volume even on a moderately restricted fluid intake . . . It is difficult to state how much fluid should be administered . . . It may be well to administer a fairly large volume (4,000 cc.*) of fluid during the first twenty-four hours in an attempt to promote diuresis. Subsequently it will ordinarily be sufficient to limit parenteral fluids to one liter of 0.85 per cent solution of sodium chloride and an additional liter of 5 per cent dextrose in distilled water. It must be remembered that the quantity of sodium must be limited as well as the total volume of fluid."[9] Case I illustrates that fluid administration of this degree may result in congestive failure and pulmonary edema; Case II, who received about one-half the recommended quantity

* Phrases in parentheses inserted by author.

of fluid, developed significant fluid retention and cardiac embarrassment. It is probable that the stumbling block in most plans of fluid management is the failure to consider the endogenous production and retention of fluid.

In a review, admittedly incomplete, of the literature there was not encountered any detailed case report in which treatment consisted of strict limitation of fluids. Nor were any cases of acute toxic nephrosis encountered that were suffering from dehydration. Peters[2] does recommend restriction of fluids but this recommendation is not amplified. Styron and Leadbetter[22] caution against the "aimless administration of fluids" and advise that "the administration of fluids should be governed by the rate of renal excretion and by the level of the non-protein nitrogen and chloride."

Since manifest edema in acute toxic nephrosis represents a significant degree of fluid retention, probable increased circulating blood volume and circulatory overload, the author recommends as a general principle that fluids be restricted below the amount that will produce manifest edema. To prevent an excess of fluid retention over fluid output it is necessary to know not only the urinary output and fluid loss by other channels but also the amount of fluid liberated from the tissues. Since the latter is undeterminable, it is preferable to err on the side of restriction. The approximate daily sodium chloride need of the resting normal adult is satisfied by about 700 cc. of physiologic saline solution.[23] This amount of salt and fluid can be used as the basic intake that may be increased or decreased in accordance with the measured loss of fluid and salt or with evidences of dehydration or mounting fluid retention. Diuresis in this syndrome is not enhanced by intravenous fluids; the route of administration is a matter of clinical judgment. In Case I, vomiting was diminished by restricting oral intake and substituting the intravenous route; the opposite was true for Case II. It probably requires reiteration that intelligent handling of this problem necessitates careful determination of intake and output. Daily weighing, if possible, may be helpful although the weight may remain stationary as fluid retention counterbalances destruction of tissue. Evidences of fluid retention, plethora and circulatory overload are to be sought for repeatedly not only in the skin but also in venous distention, enlargement of the liver, alteration in heart sounds, particularly the pulmonic second sound, height of the blood pressure and pulmonary congestion.

Carbohydrate is indicated. It may be given in a concentration of 5 to 10 per cent intravenously; greater concentrations may be attempted but should be promptly abandoned if not tolerated. If oral carbohydrates are tolerated (Case II), thick gruel with sugar, jams, bananas, and other high carbohydrate foods may be tried. An adequate total caloric intake is a lesser problem in this disorder of limited duration. Consideration must be given to the amount of fluid produced in the metabolism of any ingested food; this fluid will also be retained in the body.

The varied etiology and complications of this syndrome, along with the frequent involvement of other organs or systems by the intoxicating agent, are a challenge to therapeutic ingenuity and to the principle of avoiding overtreatment. The recommended plan of restriction of fluids does not apply to shock, which may be present initially. Shock requires prompt, energetic treatment, preferably with blood or plasma. Significant blood loss, from hemorrhage or blood destruction, is to be corrected by transfusion of compatible blood. Clinical observations and animal experiments are cited[24] to the effect that immediate transfusion of compatible blood is beneficial in hemolytic transfusion reaction. (Corroborative experi-

ments are indicated in experimental carbon tetrachloride nephrosis as well. The basic unity of the clinical and pathological findings in acute toxic nephrosis would indicate that successful basic therapy would be valuable in this syndrome, whatever the initiating agent may be.) Absolute rest, mental and physical, is promoted by reassurance and sedation (avoid sodium salts in sedation); skilled nursing care is invaluable. Associated liver damage may require therapeutic consideration, and penicillin may be necessary for a complicating pneumonia or infection. The value of repeated administration of intravenous calcium gluconate (10 cc. of 10 per cent solution, several times daily) deserves further trial if liver damage is present.[4] Hemorrhagic tendency may respond to parenteral vitamin K. (Case 1.) Dietary management must be flexible and supportive treatment may be required for some time after successful initiation of diuresis. The original condition prior to the acute toxic nephrosis, as pregnancy, wounds or other surgical conditions, may have its own therapeutic problems that require integration with the management of the renal lesion. Bandaging or freezing of the crushed limb, to retard the liberation of "nephrotoxins," are advocated in crush syndrome.[2]

Prevention is the most important aspect of the problem of circulatory overload, cardiac failure and pulmonary edema. In the literature, the feature of cardiac failure receives negligible attention although Riddell[25] believes it to be the commonest cause of fatality following incompatible blood transfusion. Cardiac failure is apt to be unexpectedly abrupt (Case 1), may occur quite early, and is frequently masked by the pre-existent fluid retention and generalized toxic manifestations. Early, slow, digitalization would seem to be indicated although it was not employed in the two case histories reported. Digitalis overdosage is to be carefully guarded against in view of the impaired renal excretion. Venesection of 500 or more cc. may be helpful in relieving circulatory overload, pulmonary edema, and episodes of hypertensive encephalopathy; the latter may require morphine and spinal puncture as well. A purely speculative therapeutic suggestion is the possibility of exsanguination transfusion in the case that progresses unfavorably despite all measures. Removal of 2,500 to 3,000 cc. of the patient's blood, and replacement by an amount of whole blood that is 500 to 700 cc. less than was removed, may aid in tiding the patient over the critical period. The known frequency of transfusion reactions in kidney diseases makes this an admittedly desperate measure.

A very recent and intriguing publication[26] proposes the use of the peritoneum as a dialyzing membrane for extrarenal excretion, to tide the patient over until renal function is spontaneously restored. Inlet and outlet tubes are introduced with "minimal surgical trauma" into the peritoneal cavity and the cavity is irrigated daily by 20 to 35 liters of specially prepared Tyrode's solution. Crystalloids are thus removed from the blood with an "efficiency adequate to substitute for renal function." The authors report the successful use of this method in a fifty-one year old man who was expected to succumb to "uremia." They further remark that this method "eliminates the need of routine intravenous fluid therapy. It is unlikely that unrestricted water administration speeds the recovery of kidney function." This technic of peritoneal irrigation should also be assessed by trial in experimental acute toxic nephrosis produced by different agents. Human cases are too occasional, too sick and too complicated to lend themselves to controlled studies. More frequent use of animal experimentation is urged to determine the efficacy of the various therapeutic measures recommended in acute toxic ne-

phrosis; including the present proposal of adjusted fluid restriction as the basic therapy until spontaneous recovery ensues.

SUMMARY

Acute toxic nephrosis is a distinctive clinical syndrome, with a striking uniformity of clinical manifestations, clinical course, laboratory findings, and pathology despite a varied etiology. This discussion is restricted to the acute renal injury resulting from carbon tetrachloride poisoning, hemolytic transfusion reaction and crush syndrome. The disorder usually terminates either in death or in spontaneous, complete recovery within two weeks after the initial injury.

The details of a case of carbon tetrachloride poisoning (Case I) and a case of hemolytic transfusion reaction (Case II) are presented to illustrate the clinical and laboratory features of this syndrome. These cases are not presented as models of therapy. Rather, they reflect the lack of any specific therapy, the problems of management, and the fallacy of imputing therapeutic value to medical and surgical measures that are currently advocated. Both cases recovered spontaneously, diuresis occurring on the eleventh and twelfth day of illness, respectively. Recovery was substantially complete.

The acute renal insufficiency of this syndrome is manifested by severe impairment of excretion of water and marked depression of tubular function. The acute, initial and persistent oliguria–anuria is followed, at times very rapidly, by fluid retention, increased circulating blood volume, circulatory overload, cardiac strain, rapid cardiac failure and pulmonary edema. Azotemia and hypertension are of subsidiary importance. Both cases demonstrate clearly that the striking clinical improvement that occurred promptly after the onset of diuresis resulted from the release of retained fluid and the relief of circulatory overload. This improvement bore no relationship to the degree of azotemia or hypertension.

The generally accepted therapy of intravenous fluids in acute toxic nephrosis is challenged as being harmful as well as ineffective. Intravenous fluids, ranging from "adequate" to "massive," consistently fail to improve urinary output. The cumulative harm of excess of intake over output lies not only in aggravation of the consequences of fluid retention but also in the fact that this harm is potentiated by another, hitherto unrecognized, source of fluid retention, endogenous fluid derived from tissue destruction. Restriction of fluids, on the contrary, does not hinder the diuresis that heralds recovery. Death in acute toxic nephrosis usually occurs in from seven to eight days. Uremia is not the usual cause of death. The cardiovascular complications deserve the greater emphasis and wider recognition.

Selective tubular damage is the outstanding pathological feature of this syndrome. The objections to the therapeutic implications drawn from the pathological studies in this syndrome are stated. The pathogenesis of acute toxic nephrosis still remains obscure and the mechanism of recovery is unknown. Tubular regeneration and diuresis parallel each other although evidences of tubular dysfunction persist for months after clinical recovery.

None of the numerous medical and surgical procedures advocated in the treatment of acute toxic nephrosis has been found effective in a significant number of cases. The basic approach to the present treatment of this syndrome should therefore be the selection of a plan of management that will tide the patient over the acute renal injury and that will favor spontaneous recovery. It is believed that fluid restriction is the keystone of this plan of management. Fluids should be restricted below the amount that will produce manifest edema or aggravation of circulatory overload. An initial daily intake

of 700 cc. of physiological saline, not necessarily intravenously, is advocated; this amount should be increased or decreased as clinical observations indicate. Other features of management and various therapeutic adjuvants are discussed.

Acute toxic nephrosis can be induced experimentally by a variety of agents. Such experiments are urged to determine the efficacy of proposed therapeutic procedures and to assess the value of plans of management.

REFERENCES

1. Fishberg, Arthur M. Hypertension and Nephritis. 4th ed., Philadelphia, 1944. Lea and Febiger.
2. Peters, Johan T. Oliguria and anuria due to increased intrarenal pressure. *Ann. Int. Med.*, 23: 221, 1945.
3. Corcoran, A. C., Taylor, R. D. and Page, Irvine H. Acute toxic nephrosis. A clinical and laboratory study based on a case of carbon tetrachloride poisoning. *J.A.M.A.*, 123: 81, 1943.
4. Kugel, Victor H. Acute toxic nephrosis in carbon tetrachloride poisoning. *J. Mt. Sinai Hosp.*, 12: 440, 1945.
5. Smetana, Hans. Nephrosis due to carbon tetrachloride. *Arch. Int. Med.*, 63: 760, 1939.
6. Kilduffe, Robert A. and DeBakery, Michael. The Blood Bank and the Technique and Therapeutics of Transfusions. Pp. 481–515. St. Louis, 1942. C. V. Mosby Company.
7. Ashe, William F. and Sailer, Seaton. Fatal uremia following single exposure to carbon tetrachloride fumes. *Ohio State M. J.*, 38: 553, 1942.
8. Hadfield, Geoffrey and Garrod, Lawrence P. Recent Advances in Pathology. 4th ed., pp. 262–277. Philadelphia, 1943. The Blakiston Company.
9. War Department Technical Bulletin (TB MED 204) Complications of Blood Transfusions, War Department, Washington 25, D.C., October 24, 1945.
10. Dunn, J. Shaw. Renal lesions in two cases of crush syndrome. *Lancet*, 2: 549, 1941.
11. Chandler and Copra. Cited by Smetana.[5]
12. Strumia, Max M. Post-transfusion hemolytic reactions. *Pennsylvania M. J.*, 47: 668, 1944.
13. Bywaters. Cited by Hadfield and Garrod[8] and Dunn.[10]
14. Ravich, A. Transfusion reaction with anuria and uremia cured by unilateral renal decapsulation. *M. Rec.*, 154: 403, 1941.
15. Flo, Spencer C. and Cummings, Harwood W. Unilateral dacapsulation of kidney for transfusion oliguria. *Surgery*, 14: 216, 1942.
16. DeGowan. Cited by Fishberg[1] and Kilduffe and DeBakery.[6]
17. Daniels, Worth B., Leonard, B. W. and Holtzman, Saul. Renal insufficiency following transfusion. *J. A. M. A.*, 116: 1208, 1941.
18. Perry, William J. Carbon tetrachloride poisoning: A report of eighty-eight cases (with an S.G.O. Note). *Army M. Bull.*, 64: 70, 1942.
19. Janeway, Charles A., Berenberg, William and Hutchins, Gretchen. Indications and uses of blood, blood derivatives and blood substitutes. *M. Clin. North America*, 29: 1069, 1945.
20. Anuria. Queries and minor notes. *J. A. M. A.*, 128: 910, 1945.
21. Fluid intake after hemolytic transfusion reaction. (From the Medical Consultants Division, Surgeon General's Office). *Bull. U. S. Army M. Dept.*, 85: 29, 1945.
22. Styron, Charles W. and Leadbetter, Wyland F. The treatment of anuria. *New England J. Med.*, 230: 721, 1944.
23. Butler, Allan M. and Talbot, Nathan B. Parenteral-fluid therapy. *New England J. Med.*, 231: 585, 1944.
24. Hesse and Filatov. Cited by Kilduffe and DeBakery.[6]
25. Riddell. Cited by Kilduffe and DeBakery.[6]
26. Frank, Howard A., Seligman, Arnold M. and Fine, Jacob. Treatment of uremia after acute renal insufficiency by peritoneal irrigation. *J. A. M. A.*, 130: 703, 1946.
27. Abbott, N. E. and Shea, P. Treatment of temporary renal insufficiency (uremia) by peritoneal lavage. *Am. J. M. Sc.*, 211: 312, 1946.
28. Snapper, Isidore. Treatment of uremia. *J. A. M. A.*, 131: 251, 1946.

Enhancement of Penicillin Blood Levels in Man by Means of a New Compound, Caronamide

CHRISTOPHER C. SHAW, M.D.,† WILLIAM P. BOGER, M.D.,† J. WILLIAM CROSSON, M.D.,† WALTER W. KEMP, M.D.,* WILLIAM S. M. LING, M.D.* *and* GARFIELD G. DUNCAN, M.D.*

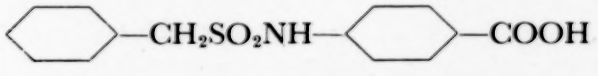
GLENOLDEN, PENNSYLVANIA

THE efficacy of penicillin as a therapeutic agent is impaired by its rapid excretion in the urine, which prevents the attainment and maintenance of high concentrations in the plasma. Relatively large doses must be administered in order to obtain detectable concentrations of penicillin in the blood stream, and massive doses of penicillin heretofore have been necessary if higher plasma concentrations are required.

The primary objective of penicillin therapy is the maintenance of therapeutic concentrations of the drug in body tissues, and it is assumed that the higher the concentration of penicillin in the plasma, the higher will be the concentration in the tissues. The commonly accepted minimal effective therapeutic level is 0.03 unit of penicillin per cc. of plasma,[1] but certain disease conditions, specifically subacute bacterial endocarditis and osteomyelitis may require much higher levels for curative effects.

Attempts to obtain high plasma concentrations (high tissue concentrations) of penicillin include: (1) increase in the dosage; (2) more frequent administration at shorter intervals; (3) variation in the route of administration; (4) attempts to slow the rate of absorption from the site of injection and (5) partial inhibition of the renal excretion of penicillin.

This report will describe a new approach to the problem of inhibition of excretion of penicillin by the kidneys by utilizing to advantage the properties and characteristics of a new compound, caronamide, which is a white, crystalline powder with the following structural formula:



Approximately 80 per cent of the penicillin in the urine is excreted by the renal tubules, while only 20 per cent of the total urinary penicillin is eliminated by glomerular filtration.[2] Any agent, therefore, which is capable of suppressing the tubular excretion of penicillin without toxic manifestations should be of value in raising the level of penicillin in the plasma.

The radio-opaque medium, diodrast, frequently employed in urography and also used for determining the functional capacity of the renal tubules, is capable of suppressing the tubular excretion of penicillin.[3] Sodium para-aminohippurate (PAH), which is also used frequently to determine renal function, will likewise suppress excretion of penicillin by the kidney tubules.[4] In other words, these two substances, both of which

† From the Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.
* From the Department of Medicine, The Pennsylvania Hospital, Philadelphia, Pa.

are excreted by the renal tubules, will inhibit the excretion of a third substance, penicillin. The continuous intravenous administration of very large amounts of either diodrast or PAH is necessary, however, and these substances are not practical for routine use.

It has been found that a new compound, 4′-carboxyphenylmethanesulfonanilide ('Staticin' caronamide*) is capable of producing reversible inhibition of penicillin excretion by the renal tubules. Caronamide is administered orally in doses of from 1.5 to 2.0 Gm. every three hours, or from 3.0 to 4.0 Gm. every four hours, and has been found to possess a low order of toxicity. It is believed that caronamide inhibits the tubular excretion of penicillin by means of "substrate competition."[5]

Diodrast, PAH and penicillin appear to be excreted through the renal tubules by the same specific transport mechanism. The excretion of penicillin is suppressed by either diodrast or by PAH whenever one or the other of these compounds is present in the blood in very large amounts. The suppression of tubular elimination of penicillin in such cases may be considered to be on the basis of "mass action." In other words, maintenance of a high plasma concentration of either diodrast or PAH will saturate the transport mechanism for penicillin and thus suppress tubular elimination of this antibiotic.

The action of the new drug, caronamide, however, is thought to be based on an enzyme-substrate competition between penicillin and caronamide, since the latter is refractory to excretion by that enzyme-transport mechanism. When caronamide is administered either orally or parenterally, experimental studies have demonstrated that this new drug will suppress the tubular excretion of penicillin by whatever route the antibiotic is given.[6] Caronamide differs from PAH fundamentally in its mode of action since it is eliminated from the body only by glomerular filtration. This new compound, acting as a substrate, presumably "combines" with an enzyme which is thought to be required for excretion of penicillin by the renal tubules. The enzyme-transport mechanism for tubular excretion of penicillin is thus temporarily suppressed or inhibited by the presence of caronamide in the blood stream, resulting in elevation and prolongation of penicillin blood levels.

The mode of action of caronamide relates to the selective inhibition of the essential component of that transport mechanism which is required for the tubular excretion of penicillin.[7] That this process is reversible upon withdrawal of caronamide is demonstrated by the fact that the enzyme is released for resumption of its normal transport function and, following elimination of caronamide by the kidney glomeruli, penicillin is promptly excreted by the tubules in accordance with its normal pattern of renal elimination. This new compound exerts no action, at any time, on the glomerular filtration of penicillin, which continues uninhibited; nor does caronamide appear to damage the renal tubular epithelium where its inhibitory action is exerted.

Extensive laboratory investigation of the physiologic, pharmacologic, toxicologic and bacteriologic properties of caronamide seemed to justify clinical application of this new compound.[8] Accordingly, preliminary clinical studies were undertaken at The Pennsylvania Hospital, in Philadelphia, from September 1 to November 15, 1946.

Penicillin and caronamide were given by oral administration simultaneously, every four hours, to a group of six afebrile patients for a period of six consecutive days. Penicillin was given by intramuscular injection and caronamide by mouth to an additional

* 'Staticin' is the proprietary name, caronamide the non-proprietary name for 4′-carboxyphenylmethanesulfonanilide, supplied by Sharp & Dohme, Inc., Philadelphia, Pa.

five patients. The effect of caronamide by mouth on penicillin in beeswax and oil was studied in three other patients. Hospital routine was not altered in any way during the period of this clinical study; fluids were taken freely, diet was unrestricted, no antacids were used and no additional measures were employed to enhance penicillin levels other than the administration of caronamide by mouth.

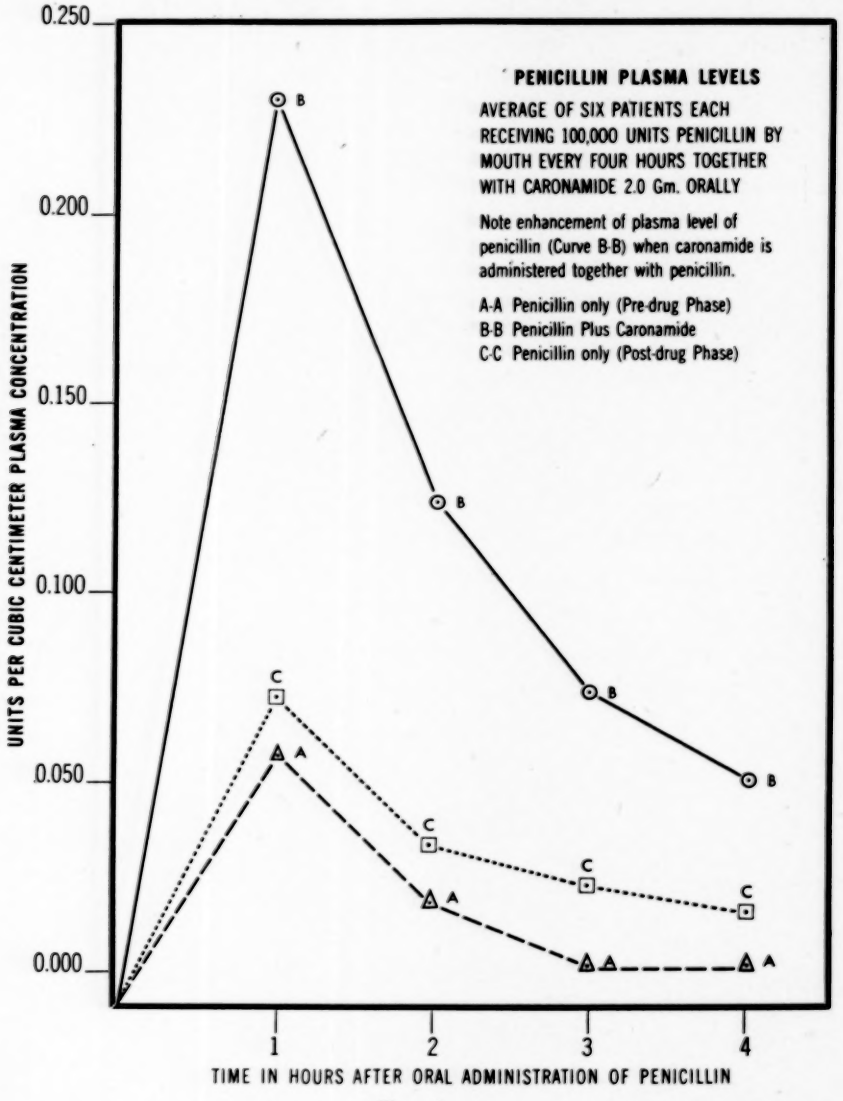


FIG. 1.

Each patient served as his own control. During the pre-drug control phase of forty-eight hours the patient received penicillin only. This was followed by a period during which the administration of penicillin was supplemented by oral caronamide (the drug phase). This, in turn, was followed by a third period when penicillin only was administered (the post-drug control phase). Thus, each patient was under observation during each phase of this clinical experiment to permit equilibration of penicillin alone and/or penicillin plus caronamide in the body tissues. Blood specimens for penicillin assay were drawn at appropriate, comparable times during each phase of this study to provide data concerning plasma concentrations: one, two, three and four hours

following the administration of penicillin and/or penicillin plus caronamide.

Of the six patients who received penicillin by mouth in doses of 100,000 units at four-hour intervals, two showed remarkable increases in their penicillin plasma concentrations during the period of administration of 2.0 Gm. of caronamide in tablet form every four hours. Three patients showed significantly higher levels of penicillin when caronamide was administered concomitantly, while one patient failed to demonstrate any detectable level of penicillin in the plasma before, during or after the administration of penicillin with or without caronamide.

TABLE I

PENICILLIN PLASMA CONCENTRATIONS (UNITS/CC) DATA ON SIX PATIENTS RECEIVING 100,000 UNITS ORAL PENICILLIN EVERY FOUR HOURS

Pre-drug Control Phase
Penicillin 100,000 Units by Mouth

Hours	Patients						Average
	A	*B*	*C*	*D*	*E*	*F*	
1	0.044	0	0.084	0.086	0.085	0.043	0.057
2	0.022	0	0.043	.....	0.022	0	0.017
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0

Caronamide Phase
Penicillin 100,000 Units q. 4 h. by Mouth together with Caronamide 2.0 Gm. q. 4 h., orally

Hours	Patients						Average
	A	*B*	*C*	*D*	*E*	*F*	
1	0.341	0	0.086	0.170	0.258	0.515	0.230
2	0.341	0	0.021	0.043	0.085	0.256	0.124
3	0.258	0	0.021	0.021	0	0.128	0.071
4	0.171	0	0	0	0	0.129	0.050

Post-drug Control Phase
Penicillin 100,000 Units by Mouth

Hours	Patients						Average
	A	*B*	*C*	*D*	*E*	*F*	
1	0.172	0.022	0.043	0.021	0.043	0.128	0.071
2	0.128	0	0.021	0	0	0.043	0.032
3	0.086	0	0	0	0	0.043	0.021
4	0.043	0	0.021	0	0	0.021	0.014

A composite curve demonstrating the relative increase in plasma levels of penicillin is presented in Figure 1. Values from which this curve was obtained are given in Table I.

In the five patients who received intramuscular penicillin and oral caronamide the same general plan of study was followed. The enhancement of penicillin levels by oral administration of caronamide averaged 5.7 times the penicillin plasma levels when caronamide was not administered. From this study it was found that 2.0 Gm. of oral caronamide every three or four hours produced a significant increase in the level of plasma penicillin when the antibiotic was given in aqueous solution intramuscularly.

In regard to the three patients who received penicillin in beeswax and oil by intramuscular injection, it was found that caronamide also increased the plasma concentration of the antibiotic agent, but the effect of a single orally administered dose of caronamide is lost at the end of four hours, presumably because of continued elimination of 4′-carboxyphenylmethanesulfonanilide by glomerular filtration. In other words, the major portion of a single dose of caronamide is excreted within four hours. Hence this new drug should be given by mouth at intervals of at least four hours, preferably every three hours.

These preliminary clinical studies indicate that caronamide produces an elevation of penicillin plasma concentration whether the penicillin is administered orally or intramuscularly. Further study is indicated to determine the effect of caronamide on plasma concentrations following intramuscular administration of penicillin in beeswax and oil.

No evidence of systemic toxicity was noted in this small series of patients to whom the new compound was given. In view of the chemical structure of caronamide, however, together with extensive experience during the last twelve years with chemotherapeutic agents, some toxic manifestations in certain individuals are to be anticipated.

CONCLUSION

It has been shown that a new drug, 'Staticin' caronamide, will inhibit the renal tubular excretion of penicillin and thereby elevate the concentration of penicillin in the plasma from two- to seven-fold following the oral and/or parenteral administration of penicillin. Caronamide should be of definite clinical value in the treatment of disease conditions in which high penicillin blood levels are required.[9]

Caronamide is administered by mouth, usually in doses of 2.0 Gm. every three or four hours, concomitantly with penicillin. Given in these doses, the drug produced no evidence of renal, bone marrow or hepatic impairment, dermatitis or drug fever in this small series of patients.

REFERENCES

1. Meakins, J. C. Smith, F. and Gold, M. A. A comparative study of some commercial preparations of oral penicillin. *Canad. M. A. J.*, 55: 97–101, 1946.
2. Rake, G. and Richardson, A. P. Pharmacology of penicillin. *Ann. New York Acad. Sc.*, 48: 143–174, 1946.
3. Rammelkamp, C. H. and Bradley, S. W. Excretion of penicillin in man. *Proc. Soc. Exper. Biol. & Med.*, 53: 30–32, 1943.
4. Beyer, K. H., Flippin, H., Verwey, W. F. and Woodward, R. The effect of para-aminohippuric acid on plasma concentration of penicillin in man. *J. A. M. A.*, 126: 1007–1009, 1944.
5. Beyer, K. H. New concept of competitive inhibition of the renal tubular excretion of penicillin. *Science*, 105: 94–95, 1947.
6. Beyer, K. H., Miller, A. K., Russo, H. F., Patch, E. A. and Verwey, W. F. The inhibitory effect of caronamide on the renal elimination of penicillin. *Am. J. Physiol.*, 149: 355, 1947.
7. Beyer, K. H., Russo, H. F., Patch, E. A., Tillson, E. K. and Shaner, G. Caronamide: its pharmacologic properties. (To be published.)
8. Crosson, J. W., Boger, W. P., Shaw, C. C. and Miller, A. K. Caronamide, a new compound for increasing penicillin plasma concentrations in man. *J. A. M. A.*, (in press).
9. Boger, W. P., Kay, C. F., Eisman, S. H. and Yeoman, E. E. High penicillin plasma concentrations by the use of caronamide, a compound that inhibits penicillin excretion by the renal tubules. *Proc. Am. Soc. Clin. Invest.*, May 5, 1947.

Review

The Syndrome of "Burning Feet" (Nutritional Melalgia) as a Manifestation of Nutritional Deficiency*

MURRAY GLUSMAN, M.D.

NEW YORK, NEW YORK

DURING the recent war with Japan "burning feet" constituted a major problem to American forces captured by the Japanese in the Philippines. At the Bilibid Prisoner of War Hospital in Manila, the central hospital for the prisoners of war on Luzon, a commission was formed to study this condition.† The author as a member of this commission and because of his special interest in neurology carried out the detailed neurologic examinations on the patients selected for special study. The commission was constantly hampered by lack of cooperation from the Japanese authorities and when these difficulties became insurmountable a brief and unsatisfactory report was submitted to the Japanese and the study was dropped. A record of the meetings of the commission, which is of historical interest only, is in the files of the Bureau of Medicine and Surgery, U. S. Navy, Washington, D. C., among the papers salvaged from the Bilibid Hospital. The original case records of this study were unfortunately destroyed by the Japanese.

† The commission consisted of the following officers: #Comdr. T. H. Hayes, M.C., U.S.N., #Comdr. Cecil C. Welch, M.C., U.S.N., Lieut. Comdr. J. Zundell, M.C., U.S.N., Lieut. Comdr. William Silliphant, M.C., U.S.N., #Lieut. Edward Ritter, Jr., M.C., U.S.N., #Lieut. Edwin Nelson, M.C. U.S.N.R., Lieut. (j.g.) M. Glusman, M.C., U.S.N.R. The ranks indicated were those held at the time this group was formed. Names preceded by # indicate members now deceased.

HISTORY

In the first British Burmese War (1823 to 1826), British military surgeons encountered a peculiar, disabling condition among the native Indian troops who were employed in the invasion of Burma. The British medical officers were unfamiliar with this condition and considered it a new entity. Reports dealing with the disorder appeared by Grierson[1] (1826), Playfair[2] (1826), Burnard[3] (1829) and McKenna[4] (1833).

Grierson, who was the first of these officers to report the condition, for want of a name simply employed the chief complaint, "a burning in the soles of the feet," in speaking of the syndrome. He observed that the condition occurred frequently after or with fever or bowel complaints but stressed the fact that it could be found apparently unconnected with any constitutional or organic disease. "It exists in various degrees of severity, from an uneasy harassing sensation of heat and tingling, to the painful extreme of burning, destructive of sleep and appetite, in the first instance, and latterly of serious injury to the general health. The sensation of heat is often experienced at the same time in the palms of the hands; and

* From the Neurological Institute of New York, The Department of Neurology and Unit of Neuropathology of the College of Physicians and Surgeons, Columbia University, New York, N. Y.

when severe in the feet, occasions an aching also along the tibiae as far as the knee. There is no inflammation, tension, discoloration, or visible change in the limb; the excruciating burning pain being the only symptom present; and the spot principally referred to as its seat, is the extremity of the foot, the heel and instep being less affected."

Burning feet became so important a problem among the native troops that the medical board of the Madras Presidency offered a prize of 500 rupees to the author of the best paper on the subject.[5] The prize was won by John Grant Malcolmson and his observations were printed in 1835, by government order.

Malcolmson,[6] who was an astute observer, attempted to differentiate burning feet from rheumatism and beriberi. He definitely drew a connection between diet and the incidence of burning feet and made the interesting observation that "in all the places in which the disease prevails rations are issued to the troops, consisting of rice, 2 ounces of ghee* (not always used), a little salt fish and spices." He claimed that the quantity of rice issued was adequate because he had seen much of the boiled rice thrown away. He concluded that "the deficiency in the food then consisted in the want of variety, of vegetables, or fresh animal food, of which almost all classes of Madras Sepoys use a certain proportion, flour, milk, and various articles with which the natives vary their diet."

Malcolmson claimed not to have seen any cases in Europeans. He noted that the involved areas were dry and did not feel hot to the touch and remarked that some patients claimed that the pain was worse at night. Malcolmson suspected that deficient nutrition and adverse climate were factors predisposing to burning feet, consequently he made the following suggestions as to treatment: "The essential object is change of climate and a return to the usual habits of life and food of the Sepoy. . . . As the patient gains flesh, and strength, the pains and burning leave him, and he recovers without the aid of medicine." He felt that because of the practical difficulties involved in supplying extensive expeditions there was no point in recommending other types of food for the troops.

Following Malcolmson's observations burning feet received scanty and rather sporadic attention until comparatively recent times. Waring[7] in 1860, added little to what the earlier writers had said. Collas[5] (1861) discussed the history of burning feet, suggested the name "causalgésie" or causalgia for the condition and attempted to differentiate it from an affliction called pedionalgia or chiropodalgia which had been observed in Piedmont in 1762. LeRoy de Méricourt[8] (1870) reviewed the work of the earlier writers and concluded that burning feet was a manifestation of beriberi.

In 1881, burning feet, under the name of "ignipedites," received brief notice from Ram,[9] Shah[10] and Naidoo[11] who indicated that the condition was still endemic in India. In 1904, Gerrard[12] added still another name when he described burning feet in Tamil laborers of Malaya and classified the condition under the heading "erythromelalgia tropica." Gerrard was impressed by the resemblance of the pain in burning feet to that in erythromelalgia. Redness, however, is characteristic of the painful limbs in erythromelalgia and S. Weir Mitchell[13] indicated this when he described and named erythromelalgia. Gerrard's patients lacked redness but his explanation was that this feature was obscured to some degree by the dark skins of his native patients.

Beginning in 1927, there was something of a revival of interest in burning feet. La-

* Ghee is a specially prepared type of butter used by the Hindus. It is derived from cow's milk or water buffalo milk.

bernadie[14] (1927) discussed the condition and claimed it was due to a non-specific polyneuritis. Dugdale[15] (1928), Galloway[16] (1928), Coope[17] (1928) and Morgan[18] (1929) reported the condition in laborers on Malayan estates, while Sharples[19] (1929) described the same manifestations in the South American sugar plantations of British Guiana. The estate and plantation physicians attempted to link the condition to dietary deficiencies in the coolie laborers.

Burning feet appeared in Europe during the Spanish Civil War of 1936 to 1939. Peraita[20] referred to it as the "paresthetic-causalgic syndrome" and he discussed at length the appearance of this condition as it developed in association with malnutrition in Madrid in 1937 and 1938. He differentiated it from beriberi and from his results with therapy claimed that the syndrome was due to the deficiency of some factor present in yeast.

In the past year burning feet has again attracted notice. Gopalan[21] (1946), working in India, described the condition and studied the effects of therapy in a series of patients. He obtained striking results with pantothenic acid. Because of its significance, Gopalan's work will be referred to in more detail later.

Still more recently, a series of reports has appeared in the literature describing experiences with burning feet among allied prisoners of war in widely scattered Japanese prison camps. In general, these reports indicate an extremely high incidence of burning feet in the deficiency states encountered in the prisoners of war. Katz[22] reported his experiences with the condition in American prisoners of war at Cabanatuan in the Philippines and estimated that 2,000 instances of what the men called "hot foot and hand disease" were observed from January to June, 1943. Gottlieb[23] described the condition in patients at the Shinagawa Prisoner of War Hospital in Tokyo. Smith[24] mentioned 700 instances of "electric feet" or "burning feet" which appeared in Hong Kong in a civilian internment camp with a population of 2,500. Harrison[25] claimed that "the outstanding symptom of nutritional deficiency in prisoners-of-war in Hong Kong was painful feet." Simpson[26] and independently Dunlop[27] described burning feet in prisoner of war camps in Java. Simpson reported an incidence of 200 to 300 patients in the average camp of 1,500 to 2,000 men, while Dunlop estimated involvement of as many as one third of the prisoners of war. Cruikshank[28] reported a study of 500 patients at the "Changi" camp in Singapore. Coates[29] described the syndrome in prisoners of war in Burma while Stenning[30] claimed that eighty-five of 300 men, an incidence of 28 per cent, were affected in a camp in Japan.

CLINICAL PICTURE AND EXPERIENCES WITH BURNING FEET

The following account deals with the author's experiences with burning feet among prisoners of war in the Philippines and Japan. The Philippine observations relate to the Bilibid Prisoner of War Hospital in Manila and Cabanatuan, the central camp for prisoners of war on Luzon. The Japanese experiences relate to the Stadium Hospital in Osaka and the Kobe Prisoner of War Hospital.

Burning Feet in the Philippines. Although the war in the Far East began in December, 1941, and evidence of weight loss and malnutrition soon became apparent among the American troops in the Philippines, it was not until July or August, 1942, three or four months after the surrender of the Americans, that the first patients with burning feet began to appear. The incidence of this condition rapidly increased until in November and December, 1942, it constituted a major epidemic. Toward the end of 1942,

at the Bilibid Prisoner of War Hospital in Manila approximately 300 of some 800 patients hospitalized for various causes complained of burning feet. Since Bilibid drew its patients from camps scattered throughout Luzon the incidence of this condition at Bilibid reflected the widespread appearance of the syndrome in the Luzon camps. The occurrence of some 2,000 such cases at Cabanatuan from January to June, 1943, has already been mentioned. There were numerous evidences of malnutrition and avitaminosis among the prisoners of war at this time. Various degrees of weight loss and ankle edema were seen. Typical pellagra rashes were extremely common. Fissuring at the corners of the mouth, glossitis, scrotal dermatitis, night blindness, corneal ulcerations, amblyopia with constriction of visual fields and central scotomata were all very common. Diarrhea, whether on a pellagrous, parasitic or bacillary basis, was practically universal. Burning feet frequently occurred in conjunction with one of these manifestations or developed in patients who either had or later developed evidences of these deficiencies. However, the striking thing appeared to be that it could occur as a distinct symptom complex by itself.

The onset of this condition was gradual with subjective complaints of numbness, pins-and-needles or tingling in the toes and feet. As a rule these occurred bilaterally. After a week or two the paresthesias gradually gave way to burning pains in the toes and soles of the feet. In more severe cases, after a variable period of days or weeks, patients began to complain of typical, sharp, periodic shooting pains. These pains did not replace the burning sensation but occurred as an added phenomenon in severe cases. The shooting pains generally radiated from the dorsa of the feet between the first and second toes up the legs in a severe, shock-like fashion. An interesting and striking phenomenon was the definite relationship of both the burning and lancinating pains to the time of day. Patients practically always complained that pains were worse at night than during the day. Beginning in the late afternoon the pains would gradually increase in severity until at bedtime sleep would be impossible. After reaching maximum intensity late at night or early in the morning, the pains would gradually subside, although rarely disappear, until the beginning of the next torturing cycle.

In severe cases the patients also occasionally complained of pains in the palms of the hands. This, too, was bilateral. Pains in the hands were not nearly as frequent as foot pains and when present, in the author's experience, they were never as severe as foot pains. Furthermore, the author never saw a patient who had only his hands involved.

In some patients, during severe paroxysms of the pain, sweating of the affected parts was noted. The sweating involved the parts in which the patient complained of the most severe pains. It was quite definite and striking and appeared fairly well delineated. The foot, particularly its distal portion, was involved. During the paroxysms of pain and sweating the involved areas felt somewhat cooler than normal to the touch. However, except for occasional slight pallor, they showed no color changes. In the author's experience the affected parts did not become red or cyanotic. This is in agreement with the experience of many observers although others claim to have found varying degrees of redness and cyanosis of the feet and hands.

Quite as striking as the cyclical character of the pain was the relief of pain with cold water. Patients practically always discovered for themselves that some degree of relief could be obtained by soaking their feet in cold water. This they frequently did several times a day. A cold shower at bedtime was another method of obtaining some relief.

Although these measures did not abolish the pain completely, they did make the condition more bearable. Conversely, heat and warm water seemed to aggravate the pain.

Plantar hyperesthesia and hyperalgesia were universal phenomena in all but the earliest and mildest cases. In moderately severe cases touching or scratching the sole of the foot caused unbearable pain. Strangely enough, when slight pressure was slowly and gently applied to the sole of the foot the patient did not complain of pain. Indeed, one of the common methods of obtaining some relief was the simple procedure that the patients adopted of clasping the distal portions of their feet in their hands and applying cautious and gentle pressure. In contrast to this was the sharp withdrawal and agonized cry of pain when the examiner attempted to elicit the Babinski sign. Fortunately, bed clothes were no problem since in the warm weather of the Philippines these were not necessary.

The condition as just described was a chronic one; nevertheless, on examination the deep tendon jerks were preserved. Occasionally, knee jerks and somewhat more frequently ankle jerks appeared diminished but preservation of reflexes was the rule. With exceptions which will be given later, spinal cord involvement did not occur. At Bilibid evidence of pyramidal tract disease was not seen. Hoffman, Babinski and confirmatory signs were negative. Knee and ankle clonus could not be elicted. There was no spasticity. Motor power was preserved. There was no paralysis of the lower extremities. The patients showed no evidence of foot drop. Even in the most severe cases, when the patients were sufficiently coaxed to disregard the pain involved in these tests they could be induced to stand on their toes or their heels.

The gait was peculiar but this appeared to be due to pain and hypersensitivity of the soles of the feet rather than to disturbance of motor power or equilibrium. The patient walked as if the ground beneath the soles of his feet were hot. He walked cautiously, gingerly, and on a somewhat widened base. Because of his reluctance to use his oversensitive toes to grip the ground, the gait had a characteristic flat-footed quality. In standing, patients frequently shifted their weight from one foot to the other in a restless and repetitious fashion. It seemed as if they could not endure the discomfort of resting their weight on one foot for more than a few moments at a time. The same restlessness was frequently noted while the patient was in bed. Often when the pain was severe patients would sit cross legged in bed, holding the distal portions of their feet in their hands and rock rhythmically backward and forward with the pain. This last attitude was not only pitiful but it was so pathognomonic that any observer walking into a ward could pick out those with burning feet at a glance.

Careful sensory examination generally revealed some degree of objective sensory involvement in marked conditions. The involvement was bilateral. Proximal to the zone of hyperalgesia and hyperesthesia, sensory diminution could be demonstrated for variable distances up the legs and even as high as the mid-thigh. Diminished sensibility was more severe distally and gradually decreased to an indefinite border proximally. Diminution of sensation rather than complete loss was the rule. The author did not see complete or clearcut anesthesia. All forms of sensation were involved. The involvement was uniform, not patchy. Occasionally the involvement assumed the sock or stocking type of distribution, at other times the upper limit of involvement, which was difficult to map accurately because it was never clearcut, was irregular in outline, not conforming accurately to either segmental or peripheral nerve patterns. As for the various sensory modalities, decrease of

pain and touch proximal to the hyperalgesia and hyperesthesia could usually be readily demonstrated. Sense of position, if at all involved, was only mildly diminished and then only in the toes. Diminished vibratory sensibility not infrequently could be demonstrated in the ankles and toes. Impairment of appreciation of hot and cold could usually be determined somewhat more easily than impairment of the other forms of sensation.

Despite the fact that this condition frequently persisted for years trophic changes were not remarkable. Katz,[22] who described burning feet in American prisoners of war at Cabanatuan, noted atrophic, thin, tightly stretched skin in the hands and feet of some patients. Trophic changes of this order have not been reported by other observers and the author from his own experience cannot confirm Katz's observations.

The condition of the musculature appeared to depend on the general nutritional state of the patient. With evidence of marked weight loss there was generalized wasting of muscle, otherwise loss of muscle was not striking. An exception to this was a moderate degree of atrophy in the intrinsic muscles of the feet which was often demonstrable in those patients with moderately severe involvement. It is possible that this was due to atrophy of disuse resulting from the disinclination to use the toes in walking. The dorsalis pedis and posterior tibial arteries in these patients were always patent and readily palpable.

Results with Therapy. Attempts at therapy were disappointing. Nicotinic acid, 100 mg. by mouth per day for ten days, dramatically relieved associated signs of pellagra but was without effect on the symptoms of burning feet. Thiamin chloride was available only at irregular intervals but the impression gained from its use was that parenteral doses up to 50 mgm. per day were not particularly effective. Controlled studies on other members of the vitamin B complex could not be undertaken because these vitamins were not available in adequate amounts. Quinine sulfate in doses of 1 to 1.3 Gm. per day by mouth seemed to ease the pain slightly in some patients. Analgesics were only mildly effective and as a rule the only real relief obtained was with narcotics. In two patients procaine infiltration of the posterior tibial nerve at the medial malleolus was attempted. This procedure relieved the pain. Coates[29] has reported relief in one patient by the more drastic procedure of section of the tibial and superficial peroneal nerves.

This description is essentially the picture of the condition as the author saw it in the Philippines among American prisoners of war. It is possible that this represented only the initial stage of a more extensive neurologic syndrome which for complete evolution requires poorer dietary conditions than those that were present in the Philippines. In support of this possibility is information the author has received that one of his patients with burning feet eventually developed signs of spinal cord involvement.[50] Urinary sphincter disturbance and signs of pyramidal tract and posterior column involvement appeared. Similarly, Cruikshank[28] at Singapore noted the development of spastic paraplegia and quadriplegia with definite signs of upper motor neuron involvement in a few of his patients with painful feet.

Burning Feet in the Hong Kong, Singapore and Java Camps; and the Diet. It is rather remarkable that burning feet appeared almost simultaneously in such widely separated areas as Hong Kong, Singapore, Java and the Philippines. Smith[24] dated the onset for a Hong Kong camp as July, 1942, Cruikshank[28] noted it the end of July, 1942, in Changi in Singapore, and Simpson[26] recognized the appearance of the condition in July, 1942, in the Java camps. The onset at Bilibid has already been noted. Following

the onset at Bilibid the number of new patients rapidly increased through the fall of 1942, reached a maximum in the winter of 1942, and then declined after the arrival of Red Cross food parcels* and some bulk food at the end of December, 1942. The decline appeared to be maintained by generally improved food conditions through the first half of 1943. Cruikshank[28] noted a similar rise at Changi in Singapore with an abrupt drop in the number of new patients following the arrival of Red Cross supplies and generally improved dietary conditions in November, 1942.

The diets which have been reported from these areas are very similar. For the Java camps Simpson[26] listed the diet as "polished rice—400 g., vegetables 200–250 g., meat—50 g., bread 50 g., coconut oil—10 g., salt—5 g." Smith[24] indicated a similar diet for his Hong Kong camp but did not give the quantities of the individual constituents. At Bilibid the diet from which burning feet developed was essentially the same as the Java camp diet. The total quantity of rice and the degree of milling varied from time to time. The meat was replaced by fish or omitted periodically and the vegetables were usually leafy greens. At Bilibid the vegetables were invariably boiled and the rice was cooked either dry or as gruel.

Paucity of New Patients and the Diet in Japan. In Japan while at the Kobe Prisoner of War Hospital† the author did not see any new patients with burning feet. There was a report of several supposedly new cases which developed in the Netherlands East Indies troops in a camp in the Osaka command and the author did see a few instances of recurrence in patients who first developed the condition in the southern areas (the Philippines, Hong Kong, Singapore, etc.). However, the paucity of new patients and the low rate of relapse of old patients in the Osaka area was rather surprising. In this region of Japan the diet differed from that noted for the Java and southern camps in one significant respect. The major portion of the southern diet consisted of only one grain and this was rice, whereas in the Osaka camps varying proportions of barley, millet seed and soya beans were always issued with the rice. It is possible that these constituents to some extent protected against the development of burning feet by supplying a factor which was deficient in the single grain (rice) diets. Gottlieb[23] and Stenning[30] reported burning feet in prisoners of war in Japan, but it is difficult to evaluate their experiences in this matter since these authors did not specify whether they were dealing with patients who developed the condition in Japan or patients who had developed the syndrome in the southern regions and were still suffering with the condition on arrival in Japan.

Development of Gangrene in Japan. A second observation of interest in the Osaka command camps, and this has been noted by Gottlieb[23] and Stenning[30] in other areas of Japan, was the occurrence of several cases of what the Japanese called "spontaneous gangrene." This developed in the toes and distal portions of the feet in a small number of patients with burning feet and required amputation of the distal portion of the involved extremity. In connection with the patients that developed gangrene it is important again to mention the pernicious habit which the patients with burning feet

* A sample parcel from the American Red Cross contained the following items: 14½ oz. tin evaporated, irradiated milk; 8 oz. pkg. biscuits; 8 oz. pkg. Borden's American cheese; 8 oz. tin instant cocoa; 15 oz. tin sardines; 1 lb. tin oleomargarine with vitamin A; 12 oz. tin corned beef; 12 oz. tin sweet chocolate; 2 oz. pkg. granulated sugar; 7 oz. tin powdered orange concentrate (vitamin C); 5 oz. pkg. dehydrated soup; 16 oz. pkg. prunes; 4 oz. tin instant coffee. Each individual received the equivalent of two and one-half parcels.

† The Kobe Prisoner of War Hospital drew patients from the camps in the Osaka command. This included some twenty camps scattered from the east to the west coast of central Honshu, with a total population of approximately 10,000 prisoners of war. The nationalities represented in these camps were British, American, Australian, Dutch, Javanese, Eurasian and Canadian.

practiced, that of obtaining relief by means of chilling the feet. In Japan they frequently walked the brick floors of the huts or barracks barefooted at night, despite the fact that the camps were practically unheated and the winters were so severe that several inches of snow were present in the camps on the east coast and several feet of snow in those on the west coast of Central Honshu. Frostbite may very well have been a factor in the production of this gangrene, these patients perhaps being more susceptible to frostbite than others. The amputations were always low, just above the gangrenous region, the wounds healed slowly but the stumps remained healthy and re-amputation was not required.

Unfortunately, it was impossible to carry out pathologic studies on the surgical sections or on patients who died of intercurrent disease. In February, 1945, however, Dr. R. Kinosita, Professor of Pathology at the Osaka Imperial University, supplied some information on the pathologic features of this condition. Kinosita[32] claimed that the Japanese had been unfamiliar with the syndrome of burning feet before the war. However, they began to see patients with this condition among the Japanese military personnel who had been cut off by allied operations in the southern battle areas for variable periods of time before rescue. These patients while in the "by-passed" regions had subsisted on reduced rations but details of their diet for purposes of comparison with that of the prisoners of war were unobtainable. Kinosita claimed to have autopsied a small number of these Japanese patients with burning feet who died of intercurrent conditions such as tuberculosis, etc., and he observed that the spinal cords and peripheral nerves in these patients were normal. He did find changes in the small arteries, whose walls were diffusely thickened, and he commented on the absence of new vessels. Kinosita also noted that gangrene did not develop among Japanese with burning feet while these patients were in the southern areas. Several patients did develop gangrene after their return to Japan.

COMMENT

For well over a century since Grierson's[1] description of the syndrome in 1826, burning feet received only sporadic attention in journals of tropical disease. For those who have not had any direct experience with the condition it has remained an obscure tropical affliction consigned to a few lines of small print in tropical disease texts. Peraita's[20] observations during the Spanish Civil War, however, and the recent reports dealing with Japanese prisoners of war indicate that when proper circumstances of malnutrition prevail this syndrome may appear in very high incidence and affect large segments of the population. Certainly in the regions mentioned burning feet exceeded classical dry beriberi as a deficiency manifestation, both in frequency of occurrence and in anguish caused the patient. From the standpoint of potential numerical significance alone, burning feet is deserving of further study. Other aspects of this disorder make the entire problem one of great interest.

Relationship to Vitamin Deficiency. A review of the existing literature on burning feet has revealed remarkably consistent descriptions of this condition by different authors. The association with malnutrition and a poor diet has been invariable and a close relationship with B complex deficiency, such as ariboflavinosis and pellagra, has been mentioned repeatedly.

The author has mentioned the frequent occurrence of other evidences of malnutrition in association with burning feet at Bilibid and this point should be stressed. Patients who developed burning feet at one time or another often presented pellagra rashes, scrotal dermatitis, glossitis, fissuring at the corners of the mouth, corneal ulcera-

tions, visual diminution with central and paracentral scotomata, ankle edema and diarrhea. The syndrome of burning feet has been described by itself because none of these associated signs seemed to be essential concomitants. Frequently these associated signs disappeared with treatment or some dietary variation which did not influence the course of the pain. Landor and Pallister[31] described a deficiency syndrome in Malayan prisons which they called avitaminosis B_2 since the manifestations responded to treatment with autoclaved yeast or marmite. In this syndrome they included scrotal eczema, superficial glossitis, eczema of the angles of the mouth, foot pains, poor vision (due to retrobulbar neuritis) and combined degeneration of the cord. Stannus,[33] although he admitted the possible rôle of other deficiencies, suggested that this syndrome including the foot pains was due to hyporiboflavinosis. There is no proof that the entire Landor and Pallister syndrome is due to riboflavin deficiency or, in fact, that it is due to any single deficiency. The response to autoclaved yeast simply indicates response to the heat-stable factors in the vitamin B complex. Riboflavin is merely one of these factors. The Landor and Pallister syndrome could well be the result of a multiple deficiency from the lack of several factors in the B complex. This is borne out by Gopalan's work which indicates that burning feet may actually be due to pantothenic acid deficiency. Gopalan[21] noted the frequent occurrence of glossitis, angular stomatitis, angular blepharitis, superficial keratitis and scrotal dermatitis in his patients with burning feet. He claimed that with riboflavin the associated signs rapidly disappeared, whereas the burning pains were unaffected. Gopalan obtained complete relief of the burning pains with vegemite, no relief with thiamin chloride or nicotinic acid, and rapid relief with calcium pantothenate. The relief with calcium pantothenate was even more impressive than the improvement with vegemite. Although Gopalan's therapeutic results with calcium pantothenate were striking, confirmation of his work and further studies on the relationship of pantothenic acid to burning feet will be necessary before a final estimate of the significance of pantothenic acid in this condition can be made.

If a relationship between pantothenic acid and burning feet can be established, this will be of some importance since the significance of pantothenic acid in human nutrition has not as yet been clarified.[34] Pantothenic acid has been known as the filtrate factor or chick antidermatitis factor.[35] It is at least one of the achromotrichia factors in the rat. Extensive neuropathologic changes due to deficiency of this factor have been demonstrated in chicks,[36] mice[37] and pigs.[38] It may be of interest at this point to call attention to some unusual symptoms that have been noted in pantothenic acid-deficient mice and pigs, although no attempt will be made to draw conclusions from these incidental findings.

Wooley[39] noted that after three weeks on a pantothenic acid-deficient diet his mice became hyperirritable and a few days later they "seemed to be seized by periodic spasms of pain, for at intervals very violent and rapid movement would take place and the animals would squeal occasionally, as if in pain." This behavior lasted a few days and then the violent movements subsided and paralysis of the hind legs developed. In speaking of pantothenic acid deficiency in the pig, Follis and Wintrobe[40] stated that "one of the first signs of neurological involvement is a sudden lifting of one of the limbs from the ground as though it were painful."

Pain in Burning Feet. There are some striking similarities between burning feet and the state which Thomas Lewis[41,42] calls erythralgia. In both conditions such phenomena as localized hyperalgesia and

burning pains which are relieved by cold and increased by heat occur. The pain in burning feet bears marked resemblances to the pain in erythromelalgia[13] and Lewis classes erythromelalgia with conditions that manifest erythralgia. Because of these similarities, it seems reasonable to suspect that the mechanisms which determine the pain in burning feet are similar to those which determine the pain in erythralgia.

In erythralgia[42] there is a generalized lowering of the pain threshold for all forms of stimuli, presumably due to a state of overirritability of the nerve endings transmitting impulses of pain. As a result of these lowered thresholds, which are manifested as localized hyperalgesia, heat elicits burning pain at considerably lower temperatures than are required in normal skin. In normal skin pain is evoked by water at a temperature of 43°C., whereas in experimentally induced erythralgia[42] and in erythromelalgia[43] temperatures of approximately 32° to 34°C. and 33° or 34°C., respectively, suffice. Since the latter temperatures are so near the ordinary range of skin temperatures such factors as the warmth of a room, the presence of bed clothes or even local vasodilatation can elevate the temperature of erythralgic skin above these lowered thresholds and thereby produce pain. Conversely, when the skin temperature falls below these thresholds, as with the action of cold water, the pain is relieved. The ease with which similar mechanisms would explain the influence of temperature on the pain in burning feet is apparent.

Furthermore, it is known that the body temperature of a given individual shows diurnal fluctuations of 0.5°F. to 1.0°F. The maximum temperature occurs in the late afternoon or early evening and the minimum occurs at approximately 4 or 5 in the morning.[44] The possible relation of this phenomenon to low pain thresholds for heat and the pain cycle in burning feet provides a point of interesting speculation. The pain in burning feet characteristically begins in the late afternoon or early evening and improves in the early morning.

Lowered pain thresholds for tissue stretch explain the influence of intravascular hydrostatic pressure on the pain in erythralgia.[42] Lewis has demonstrated that obstructing the venous return from erythralgic skin induces pain. Pain is relieved, however, if pressure is applied directly to the erythralgic skin in amounts which counterbalance the venous pressure in the cutaneous veins. Here again, an analogous situation in burning feet would explain the relief some patients obtained from gentle pressure in the foot-holding attitude described previously.

Proof of the applicability of the above mechanisms to burning feet awaits the actual determination of lowered pain thresholds in this condition. Such a demonstration would be significant from another standpoint, in that it would indicate a peripheral and local mechanism for the pain and hyperalgesia in burning feet rather than a central mechanism. Hardy, Wolf and Goodell[45] have measured the pain threshold for heat in the hyperalgesias associated with such conditions as referred pain, syringomyelia, lesions near the thalamus and in root and nerve disease. They found that, excluding hysteria and malingering, only inflammation of the skin or damage to tissue near the peripheral nerve endings for pain produced lowered pain thresholds.

Vascular Involvement. The development of gangrene in some patients in Japan points to vascular involvement in burning feet. Kinosita's claims[32] in regard to his pathologic observations are in accordance with this explanation. Sweating was observed during the paroxysms of pain in some patients and with this the feet felt somewhat cooler to the touch. However, what part the sympathetic nervous system and vasospasm played in the entire picture is difficult to

say. Skin temperatures were not accurately measured and with the exception of the instances mentioned during the paroxysms of pain, no difference could be detected by touch between the temperature of the feet in patients with burning feet and the temperature of the feet in normal individuals.

Correlation and Interpretation. Because of the lack of accurate information concerning the pathologic condition of burning feet any attempt to correlate and interpret the major phenomena in this condition must be largely speculative. Nevertheless, the underlying disorder is a nutritional one and the possibility that it may be a specific pantothenic acid deficiency must be considered. This disorder damages various susceptible tissues probably by interfering with the metabolism of these tissues. Damage to peripheral tissue in the neighborhood of the nerve endings responsible for pain, with irritation of these endings, and the production of a state similar to the erythralgic state would explain the pain in burning feet. Damage to the small arteries of the feet, as seen by Kinosita, probably reduces the circulatory efficiency of the feet and renders them susceptible to gangrene which results from repeated exposure to cold. The sensory diminution in the lower extremities indicates mild involvement of the nerves to these extremities. This involvement could be due to ischemia secondary to the circulatory impairment or it could be due to a neuropathy caused by the basic nutritional disturbance. The fact that the basic disturbance may damage nervous tissue is indicated by the development of signs of spinal cord disease in a few patients.

Burning Pains in Pellagra. The frequency with which evidence of pellagra occurred in the patients with burning feet in the Philippines has been mentioned. When patients presented both these conditions, nicotinic acid alone, without alteration of the diet, dramatically relieved the pellagra manifestations without improving the symptoms of burning feet. Burning of the soles of the feet has been described as one of the most common neurologic symptoms of pellagra.[46] Without denying that pellagra alone may produce burning foot pain, the possibility should be considered that burning pains associated with pellagra may indicate the presence of more than one deficiency state. The possible concomitant occurrence of burning feet with pellagra should be borne in mind.

Synonyms for Burning Feet. From time to time various names have been employed to denote the syndrome discussed in this paper. Generally, these have been unsatisfactory. In "Manson's Tropical Diseases"[47] a brief and confusing paragraph has been devoted to burning feet and the terms "chachaleh" and "barasheh" have been employed as synonyms. In the author's opinion these synonyms are not justified. Buchanan[48] described one hundred cases of what appears to be a mixed deficiency syndrome in natives of British Somaliland and he employed the terms "chachaleh" or "barasheh" to denote this syndrome. Burning feet was only an associated manifestation in this symptom complex since only 39 per cent of the patients had this complaint, whereas 82 per cent had edema, 41 per cent brawny edema, 60 per cent generalized aches, 53 per cent joint pains and 45 per cent complained of pains in the back of the neck and shoulders.

The name that has been most frequently used to date has been the term "burning feet." For obvious reasons this name is an unsatisfactory one. Since burning of the feet is one of the most common complaints referred to the lower extremities, the phrase burning feet may indicate a host of conditions. It fails to designate a specific syndrome. Collas[5] suggested the name causalgésie or causalgia and later Peraita used the phrase paresthetic-causalgic syndrome for what was essentially burning feet

in Madrid. The objections to these terms are that they fail to indicate the nutritional factor in the syndrome and that the word causalgia through usage implies features which are not part of burning feet. Causalgia, as derived from the Greek by S. Weir Mitchell, means burning pain. Mitchell coined this word to designate the burning pain associated with nerve injuries. With usage, however, the word has come to imply not only burning pain but a complete syndrome which follows nerve injury. Burning pain is the most prominent aspect of this syndrome but trophic skin changes such as glossy skin and a local rise in temperature are included in this picture.[49]

The condition that has been called burning feet is deserving of a better name. In the absence of such a name the author wishes to suggest the term "nutritional melalgia." The word melalgia s derived from the Greek and means limb pain. The name nutritional melalgia, therefore, indicates nutritional limb pain and expresses the major characteristics of the syndrome that has been discussed in this paper.

SUMMARY

1. The historical development of the syndrome called burning feet has been outlined.

2. The clinical features of this condition as it was seen in the Philippines and Japan have been described and experiences with this condition have been recorded.

3. The nutritional basis of the syndrome and the character of the pain have been discussed.

4. The name nutritional melalgia has been suggested to replace the original designation of burning feet.

REFERENCES

1. Grierson, J. On the burning in the feet of natives. *Tr. M. & Phys. Soc. Calcutta*, 2: 275–280, 1826.
2. Playfair, G. Letter to the editor on burning feet. *Tr. M. & Phys. Soc. Calcutta*, 2: 280, 1826.
3. Burnard, R. N. Sketch of the medical topography of Arracan, and observations on the diseases prevalent there, embracing a period from April 1, 1825 to January 20, 1826. *Tr. M. & Phys. Soc. Calcutta*, 3: 44, 1827.
4. McKenna. Extract of first half yearly report, for 1833, in article iv. On the diseases to which the native troops are peculiarly liable on the Tenasserim Coast, and in the Straits of Malacca. *Madras Q. M. J.* 1: 431–435, 1839.
5. Collas, A. M. A. Étude sur la Causalgesie (burning of the feet). Abstracted in *Ann. hyg. et de med. colon.*, 14: 828, 1911.
6. Malcolmson, J. G. Observations on Some Forms of Rheumatism Prevailing in India. Pp. 32–55. Madras, 1835. Vepery Mission Press.
7. Waring, E. J. Notes on the affection called "burning of the feet." *Madras Q. J. M. Sc.*, 1: 300–306, 1860.
8. LeRoy de Méricourt, A. Burning of the feet. *Dict. Encycl. d. Sc. Med., Par.*, 11: 318–322, 1870.
9. Ram, S. Ignipedites (correspondence). *Indian M. Gaz.*, 16: 7, 1881.
10. Shah, T. M. Ignipedites (correspondence). *Indian M. Gaz.*, 16: 64, 1881.
11. Naidoo, P. B. Cases of ignipedites. *Indian M. Gaz.*, 16: 227, 1881.
12. Gerrard, P. N. Burning foot or erythromelalgia tropica. *Dublin J. M. Sc.*, 118: 192–195, 1904.
13. Mitchell, S. W. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. *Am. J. M. Sc.*, 26: 2–36, 1878.
14. Labernadie, V. G. F. A propos d'un cas de "burning of the feet." *Tr. Far Eastern A. Trop. Med.*, Seventh Congress. 1: 13–15, 1927, 1928.
15. Dugdale, J. N. "Burning feet" and other problems in estate medical practise. *Malayan M. J.*, 3: 74–76, 1928.
16. Galloway, D. In discussion on Dugdale, J. N.[15]
17. Coope, A. B. J. "Burning feet" (correspondence). *Malayan M. J.*, 3: 129, 1928.
18. Morgan, W. B. Burning feet. *Malayan M. J.*, 4: 69–70, 1929.
19. Sharples, L. R. The condition of "burning feet" or "foot burning" in labourers on sugar plantations in the Corentyne District of British Guiana. *J. Trop. Med.*, 32: 358–360, 1929.
20. Peraita, M. Neuropathien infolge mangelhafter Ernährung. *Arch. f. Psychiat.*, 114: 611–648, 1942.
21. Gopalan, C. The 'burning feet' syndrome. *Indian M. Gaz.*, 81: 22–25, 1946.
22. Katz, C. J. Neuropathologic manifestations found in a Japanese prison camp. *J. Nerv. & Ment. Dis.*, 103: 456–465, 1946.
23. Gottlieb, M. L. Impressions of a p.o.w. medical officer in Japanese concentration camps. *U. S. Nav. M. Bull.*, 46: 663–675, 1946.
24. Smith, D. A. Hong Kong: Dietary conditions in the civilian internment camp (at meeting of the Nutrition Society on nutritional experiences in prisoner-of-war and internment camps in the Far East). *Lancet*, 1: 852, 1946.
25. Harrison, G. F. Nutritional deficiency, painful feet, high blood pressure in Hong Kong. *Lancet*, 1: 961–964, 1946.
26. Simpson, J. "Burning feet" in British prisoners-of-war in the Far East. *Lancet*, 1: 959–961, 1946.
27. Dunlop, E. E. Clinical lessons from prisoner of war

hospitals in the Far East. *M. J. Australia*, 1: 761–766, 1946.
28. Cruickshank, E. K. Painful feet in prisoners-of-war in the Far East. Review of 500 cases. *Lancet*, 2: 369–372, 1946.
29. Coates, A. E. Clinical lessons from prisoner of war hospitals in the Far East (Burma and Siam). *M. J. Australia*, 1: 753–760, 1946.
30. Stenning, S. E. L. Experiences as a prisoner of war in Japan. *M. J. Australia*, 1: 773–775, 1946.
31. Landor, J. V. and Pallister, R. A. Avitaminosis B_2. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 29: 121–134, 1935.
32. Kinosta, R. Personal communication to the author.
33. Stannus, H. S. Some problems in riboflavin and allied deficiencies (Lumleian lectures, abridged). *Brit. M. J.*, 2: 103, 1944; 140, 1944.
34. Eddy, W. H. and Dalldorf, G. The Avitaminoses. 3rd ed. P. 88. Baltimore, 1944. Williams & Wilkins Co.
35. Harrow, B. Textbook of Biochemistry. 3rd ed. P. 173. Philadelphia, 1943. W. B. Saunders Co.
36. Phillips, P. H. and Engel, R. W. Some histopathologic observations on chicks deficient in the chick anti-dermatitis factor or pantothenic acid. *J. Nutrition*, 18: 227–232, 1939.
37. Lippincott, S. W. and Morris, H. P. Morphologic changes associated with pantothenic acid deficiency in the mouse. *J. Nat. Cancer Inst.*, 2: 39–46, 1941.
38. Wintrobe, M. M., Miller, M. H., Follis, R. H. Jr., Stein, H. J., Mushatt, C. and Humphreys, S. Sensory neuron degeneration in pigs. IV. Protection afforded by calcium pantothenate and pyridoxine. *J. Nutrition*, 24: 345–366, 1942.
39. Wooley, D. W. Relationship of pantothenic acid and inosital to alopecia in mice. *Proc. Soc. Exper. Biol. & Med.*, 46: 565–569, 1941.
40. Follis, R. H., Jr. and Wintrobe, M. M. A comparison of the effects of pyridoxine and pantothenic acid deficiences on the nervous tissues of swine. *J. Exper. Med.*, 81: 539–552, 1945.
41. Lewis, T. Clinical observations and experiments relating to burning pain in the extremities, and to so-called "erythromelalgia" in particular. *Clin. Sc.*, 1: 175–211, 1933.
42. Lewis, T. Pain. Pp. 57–67. New York, 1942. Macmillan Co.
43. Brown, G. E. Erythromelalgia and other disturbances of the extremities accompanied by vasodilatation and burning. *Am. J. M. Sc.*, 183: 468–485, 1932.
44. Best, C. H. and Taylor, N. B. The Physiological Basis of Medical Practice. 4th ed. P. 623. Baltimore, 1945. Williams & Wilkins Co.
45. Hardy, J. D., Wolf, H. G. and Goodell, H. Pain threshold in man. *A. Research Nerv. & Ment. Dis., Proc.* (1942), 23: 1–15, 1943.
46. Wilson, S. A. K. Neurology. P. 1,370. Baltimore, 1940. Williams & Wilkins Co.
47. Manson-Bahr, P. Manson's Tropical Diseases. 12th ed. P. 427. London, 1945. Cassell & Co. Ltd.
48. Buchanan, J. C. R. "Chachaleh" a common disease in British Somaliland, and its relation to tropical deficiency diseases. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 25: 383–397, 1932.
49. Livingston, W. K.: Pain Mechanisms. P. 87. New York, 1943. Macmillan Co.
50. Vicale, C. T. Personal communication to the author.

Seminar on Thromboembolism

Postoperative Thromboembolism*

Some Remarks on the Influence of Early Ambulation

JOHN H. POWERS, M.D.

COOPERSTOWN, NEW YORK

EARLY rising from bed and walking preclude the protracted period of inertia which traditionally follows in the wake of surgery and permit the prompt resumption of normal activity. Many postoperative complications are favorably effected by such a program. Unfortunately, the incidence of thrombosis, of suspected thrombosis, and of thrombosis and embolism together is unaltered. Fatalities from massive pulmonary embolism, however, are less common than they were before the revival of early postoperative ambulation.

In support of these statements the following clinical study of 1,519 major surgical cases is presented. All of the patients have been under the author's personal supervision or observation and, in addition, all the tables have recently been meticulously reviewed by him or by Dr. Brantley Holt to whom he is indebted for much assistance with the collection of these data.

PRELIMINARY REMARKS

In any such investigation it is imperative that the clinical charts be complete, that the data be accurately recorded and that the diagnoses be correctly tabulated and filed. Even under the most ideal circumstances, in which the patient's record is finally reviewed and the diagnoses appended at staff meeting before tabulation and filing in a record room where secretarial and clerical assistants are trained and conscientious, secondary diagnoses are occasionally not included. Hence, they are lost to any clinical study which is based only upon a perusal of the front unit sheets or punch cards. For that reason the author believes that many reports on the incidence of postoperative thrombosis and embolism, both before and after the reintroduction of early postoperative activity, may not represent the actual frequency of these complications.

Several obvious thrombotic and embolic phenomena were discovered in this review which were not recorded among the diagnoses nor tabulated in the files. Except for the critical examination of each record, these cases would not have been included and the results and conclusions would have been correspondingly invalidated by their absence.

The pattern of surgical convalescence is undergoing such fundamental reforms so rapidly that much confusion exists in the literature on the connotation of "early postoperative activity" or "ambulation." It seems desirable, therefore, to establish a uniform terminology and it is herewith suggested that the word "immediate" be applied to postoperative ambulation which begins promptly after termination of the operation and anesthesia, walking from the table to bed as some authors advocate; that "early" be reserved for those patients who

* From the Department of Surgery of the Mary Imogene Bassett Hospital, Cooperstown, N. Y.

get out of bed and walk not immediately after operation but within the first twenty-four hours; that "accelerated" be used for activity which begins on the second, third, or fourth days; and that "traditional" or "delayed" be employed when referring to postoperative walking which is not undertaken until the fifth day or after.

Such a classification will be followed from henceforth in this discussion. The term, thrombosis, will be used to signify both the bland type and thrombophlebitis.

PRESENTATION OF CLINICAL DATA

The data herein presented have been compiled from the records of 1,519 surgical patients who had been operated on at the Mary Imogene Bassett Hospital by the two senior attending surgeons, by the resident surgeons, and rarely by the interns with senior assistance. The cases are unselected and overspread a period of a little more than five years prior to October, 1946.

Six categories of major operations have been included: (1) hernioplasties of all types, (2) appendicectomy for acute appendicitis of all grades of severity with and without drainage, (3) cholecystectomy for acute and chronic cholecystitis and cholelithiasis with and without exploration and drainage of the common duct, (4) abdominopelvic surgery for all major gynecologic abnormalities, (5) all operations on the genitourinary tract and (6) a miscellaneous group of abdominal cases, gastrointestinal, colonic and abdominoperineal resections, thoracic procedures, radical mastectomies, thyroidectomies and operations on extremities with internal fixation of both recent and old fractures.

The patients in each of these major operative groups separate themselves on a temporal basis of postoperative activity into subgroups representing early, accelerated and delayed ambulation. (Table I.) "Early" connotes rising from bed and walking within a period of six to twenty-four hours after operation; "accelerated" indicates ambulation on the second, third or fourth day. "Traditional" implies delayed activity; these patients spent an average of 12.1 days in bed. The author has had no experience with "immediate" postoperative ambulation.

In each major operative group there were one or two deaths not from embolism, seven among the urologic patients within a few hours to a few days after emergency operations for acute lesions or radical procedures for advanced disease in elderly patients. These are included in the total mortality but have not been considered when compiling the incidence of thrombosis and embolism, or the mortality from pulmonary embolism, coincidental with early, accelerated or delayed convalescence. There were also 116 children under thirteen years of age in the total series who likewise are not included in the statistics on thromboembolism. (Table II.)

All the data are presented in tabular form in Table II which requires very little additional explanation. In some cases the clinical diagnoses of thrombosis and embolism were obvious, in a few they were proved by postmortem examination and in still others they could only be suspected. Suspicion, however, was in all cases well founded. In thrombosis of the deep veins of the legs it was based always upon two, at least, of the signs characteristic of this complication, namely, pain, discomfort, soreness, or tenderness in the calves of the legs, thickening or induration of the muscles of the calves, edema or swelling of the legs or ankles, increased prominence of the superficial veins, elevation of the cutaneous temperature and a positive dorsiflexion sign (Homans' sign), usually accompanied by a low grade fever and very often by an elevation of pulse rate above the curve representing the temperature. In a few instances

the evidence was transitory in character but was of sufficient significance, in the opinion of the author, to justify the diagnosis of probable or suspected thrombosis. Hence it is believed that these patients with even minimal signs should be included in this study of the incidence of thromboembolism for it is now well established that clinically unrecognizable bland thrombosis of the deep veins of the legs occurs many times among elderly surgical and medical patients who are confined to bed.[1]

Unlike Blodgett and Beattie[2] the author does not include thrombosis even as a probable diagnosis in cases of embolism in which no thrombosis is manifest. Its existence is presupposed when embolism occurs in patients with no cardiac disease but the diagnosis should not be made unless it can be supported by clinical symptoms and signs.

TABLE I

TABULATION OF ALL THE CASES UPON WHICH THIS STUDY IS BASED

Postoperative Activity	Operations						
	Hernioplasties	Appendicectomies	Operations on Biliary Tract	Abdominopelvic Cases	Operations on Genitourinary Tract	Miscellaneous Cases	Total
Early ambulation (ambulatory within 6–24 hours after operation)	116	68	65	70	116	102	537
Accelerated activity (ambulatory 2nd, 3rd or 4th day)	14	11	25	26	91	37	204
Traditional convalescence (average of 12.1 days in bed)	75	109	92	200	89	82	647
Died—not up (within a few hours to a few days after operation)	2	2	1	1	7	2	15
Children under 13 years of age	42	42	0	0	6	26	116
Total	249	232	183	297	309	249	1519

The occurrence of probable or suspected embolism was supported in all cases by sudden pain in the chest, aggravated by breathing, usually followed by fever for three to four days, and often by a little fluid in the pleural cavity. When these signs were accompanied by hemoptysis, with or without the demonstration of a wedge-shaped shadow in the periphery of the pulmonary field by roentgenographic examination, a definite diagnosis of pulmonary embolism was made, even though the source of the thrombus was not apparent.

There were eleven patients in the first category and one in the second.

Among the patients who were ambulatory within twenty-four hours after operation and discharged from the hospital a few days later there were four who developed thrombosis and one who had both thrombosis and embolism at home. Had these patients returned to the care of family physicians in distant communities these cases might well not have been reported and hence lost to any statistical study on the incidence of postoperative thromboembolism. Early discharge from the hospital is common in clinics where patients are ambulatory on the first postoperative day and the above situation often repeated and not reported to the operating surgeon or to the hospital may account in part for the low incidence of thromboembolic complications recorded by

some authors after early postoperative activity.

In the series herein discussed the incidence of thromboembolism among the patients who were out of bed and walking within twenty-four hours after operation was 5.8 per cent and the mortality from fatal embolism was 0.56 per cent; among the patients who were ambulatory on the second, third or fourth days the incidence was 6.8 per cent and the mortality 0.49 per cent. In the control group of 642 patients who remained in bed for an average period of 12.1 days the incidence of thromboembolism was 5.4 per cent, very comparable to that in the two series in which earlier activation was permitted; the mortality from fatal embolism, however, was twice as great, namely, 1.08 per cent, as compared with 0.49 per cent and 0.56 per cent.

TABLE II

DETAILED TABULATION OF THE DATA FROM WHICH HAVE BEEN COMPUTED THE INCIDENCE OF THROMBOSIS AND EMBOLISM AND THE MORTALITY FROM EMBOLISM IN RELATION TO POSTOPERATIVE ACTIVITY; APPENDED ALSO ARE ADDITIONAL STATISTICS ON TOTAL MORTALITY FOR THE ENTIRE SERIES OF 1,519 CASES

Activity	Operative Grouping	Thrombosis	Embolism	Thrombosis and Embolism	Suspected Thrombosis	Suspected Embolism	Suspected Thrombosis and Embolism	Total Cases of Thromboembolism	Deaths from Other Causes	All Cases Analyzed	Incidence of Thromboembolism, %	Deaths from Embolism	Mortality from Embolism, %	Early Deaths not Previously Included	Children under 13 Years	Total Cases	Total Deaths	Total Mortality, %
Early Ambulation	Hernioplasty	2		1	1	2		6	0	116	5.2	0	0					
	Appendicectomy	1						1	0	68	1.4	0	0					
	Biliary surgery				1	1		2	3	65	3.1	0	0					
	Abdominopelvic	2			3		1	6	0	70	8.5	0	0					
	Urologic surgery	2		5				7	0	116	6.0	2	1.7					
	Miscellaneous	4	1				4	9	0	102	8.8	1	0.9					
	Total	11	1	6	5	3	5	31	3	537	5.8	3	0.56					
Accelerated Ambulation	Hernioplasty							0	1	14	0	0	0					
	Appendicectomy							0	0	11	0	0	0					
	Biliary surgery	1			1			2	1	25	8.0	0	0					
	Abdominopelvic	2						2	0	26	7.7	0	0					
	Urologic surgery	2		3		2	1	8	2	91	8.8	1	1.1					
	Miscellaneous			1		1		2	0	37	5.4	0	0					
	Total	5	0	4	1	3	1	14	4	204	6.8	1	0.49					
Delayed Ambulation	Hernioplasty	1		2		1	1	5	2	75	6.6	1	1.3					
	Appendicectomy	1		1	1	1		4	0	109	3.7	1	0.9					
	Biliary surgery	2			2	1	1	6	3	92	6.5	1	1.1					
	Abdominopelvic	4		2	1	2	1	10	0	200	5.5	2	1.0					
	Urologic surgery			1	1		2.	4	3	89	4.5	1	1.1					
	Miscellaneous	4		1			1	6	2	82	7.3	1	1.2					
	Total	12	0	7	5	5	6	35	10	647	5.4	7	1.08					
All Cases	Total	28	1	17	11	11	12	80	17	1388	5.8	11	0.79	15	116	1519	43	2.8

(Table II.) These figures alone permit the deduction that early or accelerated postoperative activity does not alter the incidence of thromboembolism but does reduce the number of deaths from thrombi of sufficient size to precipitate fatal postoperative catastrophies.

The analysis, however, fails to indicate

and take into consideration one very important therapeutic agent which was introduced more or less concomitantly with early postoperative activity, namely, section and ligation of the femoral vein when the diagnosis of thrombosis in the deep veins of the legs is apparent. At first the operation was limited to one side if only one leg were clinically involved. With acquisition of the realization that thrombosis in the deep veins of the lower extremities is almost always bilateral, both veins have subsequently been divided and ligated, even though symptoms and signs were restricted to one side. After such a bilateral operation the author has frequently noted evidence of thrombosis become manifest later in the opposite leg, even though the superficial femoral vein had been interrupted some days previously.

TABLE III

TABULATION OF MORTALITY OF THROMBOEMBOLISM FOLLOWING NON-OPERATIVE CONSERVATIVE THERAPY AND AFTER SECTION AND LIGATION OF ONE OR BOTH FEMORAL VEINS—FLOATING AND ADHERENT THROMBI WERE FREQUENTLY ASPIRATED BY SUCTION BEFORE LIGATION OF THE VEIN

Cases	Activity			Total
	Early	Accelerated	Delayed	
Patients with thromboembolism	31	14	35	80
Not operated upon	26	12	32	70
Deaths	3	1	7	11
Mortality	11.5%	8.3%	21.9%	15.7%
Treated by operation	5	2	3	10
Deaths	0	0	0	0
Mortality	0	0	0	0

In Table III are presented data on the mortality of thromboembolism complicating early, accelerated and delayed activity, treated both by conservative measures, and by femoral section and ligation. From this tabulation it is apparent that the mortality of postoperative thrombosis is by no means eradicated by early and accelerated activity but the incidence of fatalities is definitely reduced. Although the number of patients treated by interruption of one or both femoral veins is small, the absence of fatal embolism after this type of therapy is significant and doubtless plays some rôle in the reduced mortality of thromboembolism after early and accelerated activity.

Data from which the over-all mortality in the entire group of 1,519 patients has been computed are included in Table II but have no bearing on the title of this paper and require no discussion.

ADJUNCTS TO EARLY AMBULATION

In all non-urgent operative procedures prophylaxis against thromboembolism during the convalescence should begin before the patient enters the hospital, continue during the operation, and be maintained with intensive vigor and meticulous care during the early postoperative period.

Preoperative. Reduction of weight if the patient is obese, correction of anemia if the hemoglobin and erythrocytes are below normal, injection or surgical eradication of major varices in the lower extremities, medical supervision of cardiac abnormalities, adequate amounts of carbohydrate and fruit in the diet[3] and normal physical activity are important preoperative adjuncts to early postoperative ambulation if time permits. Eventually patients may be asked to prepare for the physical ordeal of elective surgery with much the same intent that athletes train themselves for events of physical stress, namely, to develop fitness and a reserve of energy adequate for the occasion and for the prompt restoration of normal activity thereafter.

Operative. Numerous and varied circumstances may contribute to the evolution of postoperative thrombosis; to enumerate them would be but to repeat the statements

of other authors, many of which have been copied from one by another without verification and have no scientific basis in fact. Very little careful and well controlled investigation of the etiology of thrombosis has been conducted and the cause of intravascular clotting is, even today, completely obscure.

Generally accepted by most authorities are (1) the probability that postoperative thrombosis usually originates in the large veins and venous plexuses in the calves of the legs,[4] (2) that slowing of the circulation in the lower extremities, particularly retardation of the venous return, incidental to life in bed, is an important predisposing factor and (3) that the complication is more common during the later decades of life.

Since the ages of patients who require operative treatment cannot be regulated, prophylactic efforts against thrombosis during operation and the immediate convalescence thereafter must be directed toward the prevention of trauma to the deep veins of the legs when the patient is on the operating table and to stimulation of the venous circulation in the lower extremities after the operation has been completed.

The muscles of elderly patients are atrophic and those of younger individuals become flabby under anesthesia; the calves of both are easily compressed by contact with the firm, hard mattress of the operating table. Mechanical compression is readily transmitted to the deep veins of the legs, the vessels are collapsed, intimal surfaces are approximated and vascular injury may result, at least in theory. In order to obviate this contingency the author has a small pillow placed beneath the patient's thighs, of a thickness sufficient to cause slight flexion at the knees, to raise the calves just off the mattress and thereby eliminate pressure on the posterior surfaces of the legs during the operation.

Protection of the edges of the wound, care in the placement of abdominal and pelvic retractors, gentle manipulation of tissues, accurate hemostasis, strict asepsis and maintenance of an adequate blood pressure are of acknowledged and obvious prophylactic importance.

Postoperative. When the unconscious patient is returned to bed he should be placed in a semiprone position, again to obviate pressure on the posterior aspects of the legs, and also to avoid aspiration of mucus and vomitus before consciousness returns. Immediate and continued elevation of the foot of the bed 8 inches from the floor will accelerate the flow of venous blood from the lower extremities as will also frequent and regular exercises for the feet and legs which should have been explained in detail to the patient before operation. A large sign, black letters on white cardboard, attached to the foot of the bed and always in view, will serve as a constant reminder of their importance.

Some unpublished studies by Dr. Brantley Holt and the author suggest that the venous circulation in the lower extremities of elderly patients responds less well to elevation of the foot of the bed and exercises of the feet and the legs than does the circulation of younger adults, an observation which may serve to explain the greater frequency of thrombosis and embolism among patients after the age of fifty years. The prophylactic value of turning from side to side, deep breathing, coughing, the avoidance of tight dressings and binders, the elimination of Fowler's position, adequate hydration and many other postoperative adjuncts to early ambulation have been advocated by numerous writers and need not here be repeated.

However, one further prophylactic measure which has not previously been stressed is of considerable importance. Elderly patients should not be allowed to "dangle" nor to sit in a chair with knees flexed and

legs and feet dependent. When such a patient is sitting out of bed the legs should be horizontal, the *heels only* supported on a soft footstool, the *calves* in contact with *nothing*. The muscles and veins are not then subject to compression and possible vascular injury which might conceivably predispose to thrombosis.

CONCLUSION

In reality most postoperative patients are normal, healthy individuals with aseptically sutured, cleanly healing wounds. Exercises in bed, ambulation within the first twenty-four hours, prompt resumption of a normal diet and a generally accelerated convalescence permit an early return to customary activity. Unfortunately they do not favorably influence the incidence of postoperative thrombosis nor eradicate the hazard of pulmonary embolism.

REFERENCES

1. Hunter, Warren, C., Krygier, John J., Kennedy, J. Charles and Sneeden, Vinton D. Etiology and prevention of thrombosis of the deep leg veins. *Surgery*, 17: 178–190, 1945.
2. Blodgett, James B. and Beattie, Edward J. Early postoperative rising: a statistical study of hospital complications. *Surg., Gynec. & Obst.*, 82: 485–489, 1946.
3. Bancroft, Frederick W., Kugelmass, I. Newton and Stanley-Brown, Margaret. Evaluation of blood clotting factors in surgical disease. *Ann. Surg.*, 90: 161–189, 1929.
4. Homans, John. Thrombosis of the deep veins of the lower leg, causing pulmonary embolism. *New England J. Med.*, 211: 993–997, 1934.

Conference on Therapy

Treatment of Thrombophlebitis

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students, and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. WM. DEWITT ANDRUS: The subject of the conference today is the treatment of thrombophlebitis. This disease has been a source of a great deal of worry and annoyance to clinicians and is the cause of a great many tragedies. It is encountered in both medical and surgical cases. It is, therefore, of interest to all of us. The discussion will be opened by Dr. Irving Wright.

DR. IRVING WRIGHT: I may preface my remarks by saying that the treatment of thrombophlebitis constitutes one of the most controversial subjects in the field of medicine today, just as it has been for the last fifteen years. We have tried to steer a course between the two extremes, on the one hand, of prejudice and resistance to new advances in therapy and on the other, of overenthusiastic acceptance of therapeutic measures which have not seemed especially sound. Such a course has been quite difficult. Numerous forms of treatment have been suggested, many of which have enjoyed only temporary popularity. There was, for example, the plan of immediate ambulation without any supplementary measures such as venous ligation or anticoagulant therapy. The use of leeches was widely advocated abroad for many years, and to a lesser degree in this country. Lumbosacral block was advocated as a cure, and although it has proven to be of value in some patients, it is no longer regarded as a cure.

Thrombophlebitis is not a single disease. There has been an unfortunate tendency in recent years to confine the scope of discussions on this subject to thrombophlebitis in postoperative patients and further, to thrombophlebitis of the lower extremities. There are many important types of the disease. There is the one due to chemical irritants, such as arsphenamine and concentrated vitamin C solutions. Another type is due to chronic trauma, for example, persistently tying shoe laces too tightly over the arch of the foot. There is suppurative thrombophlebitis in which the infection extends from a nearby abscess or severe infection. There is thrombophlebitis associated with various blood dyscrasias, such as polycythemia and leukemia. There is the type associated with thrombo-angiitis obliterans. Frequently, it is the presenting problem in thrombo-angiitis obliterans, the underlying disease escaping recognition by the physician. There is also thrombophlebitis migrans which is relentless and frequently spreads to all parts of the venous system, ending fatally in a high percentage of patients. It is evident that the treatment of thrombophlebitis cannot be reduced to a simple routine. The treatment of each patient must be decided on the basis of the etiologic factors and the presenting pathologic changes.

In any large hospital, the largest numbers of cases of thrombophlebitis are secondary to surgical or obstetrical procedures, but in

office practice and the practice of internal medicine one frequently sees cases due to the other causes.

The difference between thrombophlebitis and phlebothrombosis has received considerable emphasis, perhaps more than it deserves. It is true that thrombi in phlebothrombosis are not fixed firmly to the walls of the veins during the early days when there is little inflammatory reaction. In most instances as time elapses they become firmly fixed and cannot be distinguished pathologically from thromboses due to thrombophlebitis. The important matter is that venous thromboses, except those due to thrombo-angiitis obliterans, are capable of producing emboli. The silent thromboses frequently produce emboli as devastating as the ones that are easy to recognize. It is impossible to predict whether or not a patient who has a thrombophlebitis in the legs is going to have a fatal pulmonary embolus; therefore, all thrombophlebitis must be regarded as serious and potentially fatal if steps are not taken to prevent the formation of emboli.

Let us consider briefly the several therapeutic measures which have long been studied, although in the case of some of them considerable doubt still prevails regarding the best procedure. I believe there is a fairly universal agreement today that, in the case of a patient with thrombophlebitis of the lower extremity with edema, elevation of the extremity is helpful in reducing the edema to a minimum. To keep the affected extremity in a dependent position or at the level of the body is of no therapeutic value and may actually be harmful.

Whether heat or cold should be applied to such patients has long been debated. The consensus at present seems to favor heat, if properly applied. I am not sure that we know how to apply it properly. The technic described by Barker is now most acceptable. The affected extremity is carefully covered with a thin layer of petrolatum or similar substance to prevent maceration of the skin and a moist, hot pack is applied. This may be in the form of turkish towels dipped in hot water, wrung out and laid loosely around the extremity which is then covered with a rubber blanket and surrounded by hot water bags. The hot pack is kept on for twenty out of twenty-four hours, allowing four hours for aeration and drying of the skin. In severe cases with marked edema, both lumbosacral sympathetic block and hot packs may be used simultaneously. The application of hot packs to an extremity immediately after lumbosacral block seems to prolong the vasodilating effect of the block, reducing vascular spasm and permitting more free drainage.

The matter of activity versus rest has long been debated and it is still unsettled. There were some who believed that one should wrap a bandage tightly around an affected leg and instruct the patient to walk forty or sixty blocks a day, if there were no symptoms. I have seen some very poor results from this form of therapy. There are those who believe in keeping the patient at complete rest in bed until signs of the disease have completely subsided, as determined by the return to normal of the sedimentation rate, blood count, heart rate and temperature. A middle course between these two extremes seems to be the present tendency. Those who have been using anticoagulant therapy have been allowing their patients up earlier, keeping them in bed between six and ten days rather than twenty-eight or thirty days.

The control of epidermophytosis is a point of very great importance in those patients with the idiopathic type of thrombophlebitis. Some believe that there is a very close causal relationship between fungus infection and thrombophlebitis of the lower extremities, either allergic or by direct

invasion of the vein by the infectious agent. Also, the fungus produces cracks in the skin which facilitate entry of secondary invaders. In many patients who have had thrombophlebitis repeatedly, recurrences are apparently prevented by the simple expedient of keeping the dermatophytosis under control.

There is one point, the importance of which I cannot emphasize too strongly, namely, that of refraining from making physical examinations of the chest in which patients are instructed to take deep breaths for the purpose of determining whether or not an infarction of the lungs has taken place or the location of the infarct. Deep breathing increases the negative pressure in the chest, thereby increasing the speed of blood flow from the extremities and which may break off the loose tails of the thrombi. If a person was operated upon ten days previously or if he has an acute phlebitis and suddenly develops a stabbing pain in the chest and coughs up some blood, it is quite probable that he has developed a pulmonary embolus. It is of minor importance to learn exactly where the infarct is. It is purely an academic question. There have been several deaths following shortly upon such examinations. So far this dangerous procedure has received only brief mention in the literature. Sliding an x-ray cassette under the patient's chest is a much safer way of locating an infarct.

A patient should also be advised against violent coughing and straining at stool, and it is up to the doctor to see that the patient does not indulge in either. There have been a number of patients with thrombophlebitis who have died during defecation. I knew one patient who died under these circumstances a month after she was discharged from the hospital, at a time when the thrombophlebitis appeared to have subsided completely.

Venous ligation as an aid in treating thrombophlebitis has had a troubled history. It appears as though its exponents have been chasing the rainbow's end from the lower saphenous vein all the way up to the superior vena cava. One of the shortcomings of treatment by ligation is that emboli may result from thrombi forming at the site of any ligation. Thrombophlebitis and varicosities also sometimes recur after ligation of the affected vein. I have a patient in the hospital now who never did have an embolus from the original thrombophlebitis, but promptly after a bilateral femoral ligation she began to have emboli and continued to have them until treated with anticoagulants. Edema may also sometimes occur following ligation. It is maintained by the exponents of ligation of the inferior vena cava that following this procedure there is less edema than is seen after femoral ligation, but on reading the reports of a few years ago one sees that some enthusiasts then maintained that there was no edema following femoral ligations. I believe there are specific indications for ligation but this procedure should not be used indiscriminately. It is indicated if there is a lesion in a lower extremity which gives rise to recurring emboli. Ligation is a much safer procedure now that anticoagulant therapy is available and anticoagulant therapy should always be used following venous ligation. Varicose veins, of course, constitute the major field for ligation and no one can dispute the importance of the operative procedure in these cases.

Now we come to another subject of considerable controversy, namely, anticoagulant therapy. Heparin was the first of the chemically effective anticoagulant agents. We have followed its use with great interest since it became available in this country for the treatment of thrombophlebitis. It prolongs the coagulation time. Statistics clearly show that it markedly reduces the number of pulmonary emboli and the number of deaths. It is administered, as most of you

know, either by continuous intravenous infusion so as to keep the coagulation time preferably between twenty and forty-five minutes, or by repeated intravenous injections of 75 mg. every three or four hours. This method produces marked fluctuations in the coagulation time, as high as one hundred minutes shortly after the injection, with a return to normal before the next injection. Dr. Loewe has been developing a menstruum which releases heparin slowly. The present menstruum for an intramuscular injection cannot be considered entirely satisfactory; its injection is extremely painful to the patient, it is difficult to control and it produces nausea in some patients, but I think it is a move in the right direction and the subject should be pursued further. There are many disadvantages in the use of heparin. It is an expensive procedure. So far, it can be administered only by injection and the danger of hemorrhage from improper use is well known. It requires close supervision by the house staff both day and night for the duration of its administration in order to check the blood coagulation time, although with the intermittent method the number of checks of coagulation time is reduced markedly.

Dicumarol has now become more popular. It is inexpensive. It can be given by oral administration. Dicumarol interferes with the production of prothrombin and it affects the coagulation time. There has been some question about the effect of dicumarol on the coagulation time and unless the test is properly made one may fail to detect a prolongation of the coagulation time. In this connection a word should be said about the Lee-White glass tube method. Some important work has recently been undertaken in a number of institutions to study the types of tubes other than glass, because it has long been recognized by those of us working in the field of peripheral vascular diseases that the glass tube Lee-White method does not even remotely represent coagulation time as it occurs in the blood vessels. I should like to quote some hitherto unpublished figures from Dr. Kadish of the Mayo Clinic. Using the Lee-White method he found the coagulation time from six to seven minutes with the glass tube, from thirteen to fourteen and even up to nineteen minutes with the lucite tube and considerably higher values with the collodion or paraffin tube. With the lucite tube the normal value of thirteen to nineteen minutes is found shortened to six to eight minutes in those patients with thrombophlebitis and prolonged to thirty to forty minutes or more in a patient taking dicumarol. Even with the glass tube, if the test is carefully performed, it can be shown that dicumarol prolongs the coagulation time but the use of the lucite tube provides a much more sensitive method for demonstrating this change. In our laboratory, however, the results with the lucite and other tubes have been too unpredictable to be used as a guide to dicumarol dosage.

Dicumarol therapy also has several disadvantages. It requires daily prothrombin tests and the laboratory must be prepared to do them. It is difficult to get laboratories to do the test accurately. As with heparin there is the risk of hemorrhage if the patient is not watched carefully. There are several gaps in our knowledge of the action of dicumarol. Work on intravascular clotting in animals is not sufficient, so our knowledge of the action of dicumarol has to advance largely by cautious experiments on man.

There are some very striking figures on the value of dicumarol therapy. One might mention those of Barker and his group at the Mayo Clinic in which they compared the results in 897 patients with thrombophlebitis treated without anticoagulant agents before emboli developed, with the results in 138 similar patients treated with dicumarol. An incidence of 10.6 per cent of subsequent thrombophlebitis or pulmonary embolism

was reduced to 2.9 per cent in the group with dicumarol; also, an incidence of 5.7 per cent of fatal pulmonary embolism was reduced to 0 per cent in those treated with dicumarol. They also made another type of analysis. They compared the results in 678 patients who had suffered one or more nonfatal embolus and did not receive anticoagulant therapy, with the results in 180 similar patients treated with dicumarol. An incidence of 43.8 per cent of subsequent thrombosis or embolus was reduced to 1.1 per cent in those treated with dicumarol; also, an incidence of 18.3 per cent of fatal pulmonary embolus was reduced to 0.6 per cent in those treated with dicumarol. It is noteworthy that substantially similar results in very large groups of patients have been reported by Jorpes and his collaborators from the Karolinska Institut in Stockholm, where they used heparin in some patients and dicumarol in others.

DR. ANDRUS: As Dr. Wright has pointed out the therapy of thrombophlebitis is complicated and none of the various methods of treatment which have been used in the past have been entirely satisfactory, but certainly a great advance has been made with the use of anticoagulant therapy. I think that perhaps the internists and surgeons, while they see the problem from a common point of view in many ways, look upon certain aspects of it somewhat differently. I will ask Dr. Glenn to discuss this problem from the surgical point of view.

DR. FRANK GLENN: To the surgeon, pulmonary embolism is always a matter of grave concern and the surgeon's attack on it must begin with the preoperative preparation of the patient and the care of the patient during the operation.

It seems to me that the care which has been exercised in the operating room in the past few years to maintain an individual's blood pressure at a proper level has been of great importance in reducing the incidence of postoperative thrombophlebitis. Permitting the blood pressure to fall to a low level and the associated shock certainly predispose to coagulation of blood, especially in the vessels of the lower extremity. The care of the patient after operation is equally important. Having the patient do exercises while in bed and employing early ambulation help to reduce the incidence of thrombophlebitis and emboli, especially those fatal emboli which arise from the lower extremity. Statistics from various laboratories of pathology show that the majority of these fatal emboli from the lower extremity arise from the deep femoral circulation. When conservative measures fail to prevent the appearance of emboli or thrombophlebitis the surgeon naturally tends to take more active steps.

There has been a great deal said about ligation. In our clinic here we do not follow in the footsteps of some of those farther up the coast who even do prophylactic ligation. Nevertheless, when one is confronted with what appears to be a thrombophlebitis with embolism, interruption of the deep circulation is certainly indicated. It should be undertaken immediately. Where one may limit treatment to the use of anticoagulant therapy alone, especially in the surgical cases, is a question that has certainly not been settled.

In tracing the history of ligation one finds that the first approach involved ligation of the superficial circulation. Division of the deep femoral circulation was not attempted until later. For the majority of patients the division of the deep femoral vessels is probably the procedure of choice. I certainly believe that following ligation of these vessels the incidence of emboli has been reduced. Along with the interruptions of the deep femoral circulation, anticoagulant therapy as already outlined, is certainly indicated. Some object to operative procedures because of the edema and disability

which may result. Generally speaking, we have found that division of the deep femoral circulation is not followed by as much edema as one is led to believe. Usually, the higher the interruption of the venous return the better is the collateral circulation which is thereafter established. If a patient has been ill for a long time or has had some surgical procedure involving one extremity and thrombophlebitis has developed, then the choice rests between a bilateral ligation of the femoral and the common iliac vessels. In patients with pelvic involvement ligation of the inferior vena cava is indicated. This is an heroic procedure and is occasionally fatal but I believe it can be utilized to good advantage if combined with anticoagulant therapy.

DR. ANDRUS: The topic today is the treatment of thrombophlebitis but I am sure that all of those interested in the subject agree that the most important aim is the prevention of thrombophlebitis. Unfortunately, our understanding of the factors which produce it is very meager. However, I think that we do know of certain measures which tend to diminish the incidence of thrombophlebitis, such as the avoidance of infection, the prevention of stasis in the veins of the legs resulting from the use of tight dressings, from distention of the abdomen or from the low blood pressure of shock. The use of deep breathing exercises prophylactically after operation has been widely employed, as well as the use of routine postoperative exercises with the patient in bed until early ambulation is feasible. Deep breathing is used to prevent venous stasis. It is certainly to be carefully avoided if thrombophlebitis is present or even suspected. No methods of prevention are universally successful. It is to be hoped that continued investigation will give us greater understanding of this complicated group of diseases and will reveal more effective means of prevention and better therapeutic agents.

Dr. Wright, will you make a few remarks on the diagnosis of thrombophlebitis? How do you demonstrate its presence?

DR. WRIGHT: I wish to say first, that I agree with Dr. Andrus in that if we keep these individuals active, get them out of bed very early, move their legs, have them exercise in bed and take deep breathing exercises the number of thrombi that will be available for pulmonary emboli will probably be markedly reduced. The diagnosis of most cases of thrombophlebitis is usually relatively easy. One of the first symptoms is pain, which is frequently along the course of a vein. One can usually see some redness along the course of the vein and detect tenseness on palpation. Sometimes the vein is still patent but often the lumen is obliterated quickly by thrombus. Sometimes there are cramps in the muscles and there is usually fever, tachycardia and increased sedimentation rate. Those are all cardinal signs; however, many patients complain of only vague pain in the calf and Homans' sign is equivocal. This sign is considered positive when pain is produced in the gastrocnemius area as the result of dorsiflexing the foot by pressure on the distal portion of the sole of the foot with the patient in the supine position. A positive sign is suggestive of thrombophlebitis, although other conditions such as strains and injuries of the soleus muscle may simulate it. The amount of pain may depend on how hard the examiner presses against the ball of the foot because one can produce pain in a normal soleus muscle by overtaxing it. I am sure there are some false Homans' signs elicited by too strenuous dorsiflexion of the foot but at any rate one must watch for the minimal signs. There are patients with marked thrombosing processes and fatal embolisms in whom there are no signs prior to the emboli.

DR. ANDRUS: As Dr. Wright said, whether a patient with thrombophlebitis should be

kept quïet or should be active has been the subject of a good deal of difference of opinion. You may be interested in the story which was told about Dr. Bloodgood at Johns Hopkins. He preached to his students most assiduously that all patients with thrombophlebitis should be kept perfectly quiet. He himself, in the course, I think, of a pneumonia for which he was treated at home, developed a thrombophlebitis. During sleep he fell out of bed and spent the next ten days on the floor, refusing to be moved. At least he was consistent and had the courage of his convictions. Dr. Wright mentioned that some compromise might be reached between complete quiet and early activity. Would you care to say a little more about where the compromise should be made?

DR. WRIGHT: In the light of our present knowledge I should say that the patient should be kept quiet until he is under adequate anticoagulant therapy. Experience at the Mayo Clinic and in Sweden indicates that these patients may be allowed out of bed with very little risk, within five days after adequate anticoagulant therapy has been established.

A word about what we consider adequate therapy. With heparin, I think, a prolongation of the coagulation time to between twenty and forty-five minutes is adequate. It is much safer than if it is allowed to go up to seventy-five minutes. Beyond this a dangerous level is reached very quickly. We have had very satisfactory results in some hundreds of patients, with the coagulation time no higher than forty-five minutes.

With dicumarol we seek to maintain the prothrombin time between thirty and fifty seconds which with the technic we use is between 20 and 10 per cent of the normal prothrombin activity. That seems to be an adequate range. Some workers believe that the anticoagulant effect is satisfactory only if the prothrombin activity is lower than 20 per cent but there is no satisfactory proof that so much depression of prothrombin activity is necessary.

DR. GOLD: Perhaps a word should be said here about the meaning of the terms "prothrombin time" and "prothrombin activity." There is a good deal of misunderstanding about them. The prothrombin content of the blood is expressed as "prothrombin activity." This may be greatly reduced before there is any striking change in blood clotting. Since the test for "prothrombin time" depends on speed of clotting this test becomes abnormal only after considerable reduction has taken place in the prothrombin content of the blood. In actual testing of the "prothrombin activity" using blood dilutions (which are in effect the same as reducing the concentrations of prothrombin) it has been found, for example, that by the time the prothrombin content has been reduced from 100 to as low as 30 per cent of the normal, clotting has been only moderately impaired as shown by the fact that the "prothrombin time" has only risen from about twelve to eighteen seconds, or a rise of only about 50 per cent. Beyond a given point, however, further reduction in the prothrombin content (prothrombin activity) begins to influence greatly blood clotting (prothrombin time) and small further reductions in the content of prothrombin begin to produce large increases in the prothrombin time; for example, a reduction of the prothrombin activity from 30 to 10 per cent of the normal, delays clotting so much that it raises the prothrombin time from 18 to 38 seconds, that is, a rise of about 100 per cent. The point of this is to emphasize the need for bearing in mind the difference between the terms "prothrombin activity" and "prothrombin time." The further point is that after a conspicuous rise in prothrombin time has taken place with dicumarol therapy, the patient must be watched carefully, for small addi-

which may result. Generally speaking, we have found that division of the deep femoral circulation is not followed by as much edema as one is led to believe. Usually, the higher the interruption of the venous return the better is the collateral circulation which is thereafter established. If a patient has been ill for a long time or has had some surgical procedure involving one extremity and thrombophlebitis has developed, then the choice rests between a bilateral ligation of the femoral and the common iliac vessels. In patients with pelvic involvement ligation of the inferior vena cava is indicated. This is an heroic procedure and is occasionally fatal but I believe it can be utilized to good advantage if combined with anticoagulant therapy.

DR. ANDRUS: The topic today is the treatment of thrombophlebitis but I am sure that all of those interested in the subject agree that the most important aim is the prevention of thrombophlebitis. Unfortunately, our understanding of the factors which produce it is very meager. However, I think that we do know of certain measures which tend to diminish the incidence of thrombophlebitis, such as the avoidance of infection, the prevention of stasis in the veins of the legs resulting from the use of tight dressings, from distention of the abdomen or from the low blood pressure of shock. The use of deep breathing exercises prophylactically after operation has been widely employed, as well as the use of routine postoperative exercises with the patient in bed until early ambulation is feasible. Deep breathing is used to prevent venous stasis. It is certainly to be carefully avoided if thrombophlebitis is present or even suspected. No methods of prevention are universally successful. It is to be hoped that continued investigation will give us greater understanding of this complicated group of diseases and will reveal more effective means of prevention and better therapeutic agents.

Dr. Wright, will you make a few remarks on the diagnosis of thrombophlebitis? How do you demonstrate its presence?

DR. WRIGHT: I wish to say first, that I agree with Dr. Andrus in that if we keep these individuals active, get them out of bed very early, move their legs, have them exercise in bed and take deep breathing exercises the number of thrombi that will be available for pulmonary emboli will probably be markedly reduced. The diagnosis of most cases of thrombophlebitis is usually relatively easy. One of the first symptoms is pain, which is frequently along the course of a vein. One can usually see some redness along the course of the vein and detect tenseness on palpation. Sometimes the vein is still patent but often the lumen is obliterated quickly by thrombus. Sometimes there are cramps in the muscles and there is usually fever, tachycardia and increased sedimentation rate. Those are all cardinal signs; however, many patients complain of only vague pain in the calf and Homans' sign is equivocal. This sign is considered positive when pain is produced in the gastrocnemius area as the result of dorsiflexing the foot by pressure on the distal portion of the sole of the foot with the patient in the supine position. A positive sign is suggestive of thrombophlebitis, although other conditions such as strains and injuries of the soleus muscle may simulate it. The amount of pain may depend on how hard the examiner presses against the ball of the foot because one can produce pain in a normal soleus muscle by overtaxing it. I am sure there are some false Homans' signs elicited by too strenuous dorsiflexion of the foot but at any rate one must watch for the minimal signs. There are patients with marked thrombosing processes and fatal embolisms in whom there are no signs prior to the emboli.

DR. ANDRUS: As Dr. Wright said, whether a patient with thrombophlebitis should be

kept quiet or should be active has been the subject of a good deal of difference of opinion. You may be interested in the story which was told about Dr. Bloodgood at Johns Hopkins. He preached to his students most assiduously that all patients with thrombophlebitis should be kept perfectly quiet. He himself, in the course, I think, of a pneumonia for which he was treated at home, developed a thrombophlebitis. During sleep he fell out of bed and spent the next ten days on the floor, refusing to be moved. At least he was consistent and had the courage of his convictions. Dr. Wright mentioned that some compromise might be reached between complete quiet and early activity. Would you care to say a little more about where the compromise should be made?

DR. WRIGHT: In the light of our present knowledge I should say that the patient should be kept quiet until he is under adequate anticoagulant therapy. Experience at the Mayo Clinic and in Sweden indicates that these patients may be allowed out of bed with very little risk, within five days after adequate anticoagulant therapy has been established.

A word about what we consider adequate therapy. With heparin, I think, a prolongation of the coagulation time to between twenty and forty-five minutes is adequate. It is much safer than if it is allowed to go up to seventy-five minutes. Beyond this a dangerous level is reached very quickly. We have had very satisfactory results in some hundreds of patients, with the coagulation time no higher than forty-five minutes.

With dicumarol we seek to maintain the prothrombin time between thirty and fifty seconds which with the technic we use is between 20 and 10 per cent of the normal prothrombin activity. That seems to be an adequate range. Some workers believe that the anticoagulant effect is satisfactory only if the prothrombin activity is lower than 20 per cent but there is no satisfactory proof that so much depression of prothrombin activity is necessary.

DR. GOLD: Perhaps a word should be said here about the meaning of the terms "prothrombin time" and "prothrombin activity." There is a good deal of misunderstanding about them. The prothrombin content of the blood is expressed as "prothrombin activity." This may be greatly reduced before there is any striking change in blood clotting. Since the test for "prothrombin time" depends on speed of clotting this test becomes abnormal only after considerable reduction has taken place in the prothrombin content of the blood. In actual testing of the "prothrombin activity" using blood dilutions (which are in effect the same as reducing the concentrations of prothrombin) it has been found, for example, that by the time the prothrombin content has been reduced from 100 to as low as 30 per cent of the normal, clotting has been only moderately impaired as shown by the fact that the "prothrombin time" has only risen from about twelve to eighteen seconds, or a rise of only about 50 per cent. Beyond a given point, however, further reduction in the prothrombin content (prothrombin activity) begins to influence greatly blood clotting (prothrombin time) and small further reductions in the content of prothrombin begin to produce large increases in the prothrombin time; for example, a reduction of the prothrombin activity from 30 to 10 per cent of the normal, delays clotting so much that it raises the prothrombin time from 18 to 38 seconds, that is, a rise of about 100 per cent. The point of this is to emphasize the need for bearing in mind the difference between the terms "prothrombin activity" and "prothrombin time." The further point is that after a conspicuous rise in prothrombin time has taken place with dicumarol therapy, the patient must be watched carefully, for small addi-

tional doses of the drug by causing further small reductions in the prothrombin content, may produce abrupt rises in the prothrombin time, blood clotting being so markedly impaired as to give rise to spontaneous hemorrhages.

In the actual carrying out of the test for the prothrombin time in the laboratory, there appear to be so many variables that it is necessary to have a control subject tested at the same time, as a means of insuring the accuracy of the test. It might be well for the physician to consult with the laboratory which performs the prothrombin test for him, in order to be sure of the precise meaning of the figures which are reported to him since the results obtained by different laboratories are somewhat different depending on the conditions of the test.

I should like to ask Dr. Wright what percentage of bed patients who develop a pulmonary embolus give evidence of thrombophlebitis prior to the embolus.

DR. WRIGHT: I do not know of any adequate figures on that point. Perhaps some of the surgical staff can answer the question more specifically.

DR. ANDRUS: After an embolism occurs you can nearly always determine where it came from, but I know of no figures on the number of patients in whom the diagnosis of thrombophlebitis is made or is possible before emboli have occurred.

DR. HAROLD E. B. PARDEE: In relation to Dr. Gold's question I think it is only in a small percentage of patients in whom one recognizes signs of thrombophlebitis prior to the embolic phenomena.

DR. GOLD: I agree with that. I have seen many cases of pulmonary embolus in nonsurgical patients but I can recall only two instances in which signs of phlebitis presented themselves prior to the embolus, to suggest the possibility of embolus. It may be that the signs of thrombophlebitis are often not very conspicuous and we do not look carefully enough in medical patients confined to bed.

DR. ANDRUS: I would certainly claim no special ability for the surgical service, for I know there are many patients in whom we recognize the thrombophlebitis only after the embolus but there are certainly a great many in which we recognize thrombophlebitis beforehand. I would guess that we recognize the phlebitis in about half of the patients before they have an embolus.

DR. WRIGHT: Do you not think that that represents a very strong teaching point, namely, our house physicians should be trained to make daily observations postoperatively on the legs of all patients? I am sure that many more of these cases would be recognized if that were a standard procedure on all surgical services.

DR. PARDEE: How long do you believe anticoagulant therapy should be continued and what criteria would you use for stopping it?

DR. WRIGHT: It depends on the type of case. We like to keep the individual who has had a simple thrombophlebitis of short duration on anticoagulant therapy for three to four weeks. I have recently been told that at the Mayo Clinic they continue dicumarol therapy for only eight to ten days and that their results have not changed with this brief therapy. We have perhaps been playing overly safe. However, we see a considerable number of patients who have thrombophlebitis for from four months to three years almost without interruption. The phlebitis is sometimes migratory and sometimes largely localized to one set of veins. It seems desirable to keep these patients on anticoagulant therapy for four weeks at least. Such prolonged treatment has been strikingly successful in interrupting chronic phlebitis.

STUDENT: How do you manage the postoperative patient who develops a hemorrhage while on the anticoagulant therapy?

DR. ANDRUS: The first thing is to discontinue the anticoagulant. By giving massive transfusions and massive doses of vitamin K, the hypoprothrombinemia associated with dicumarol can be corrected to a degree. For hemorrhage occurring during the use of heparin, protamine has been suggested for neutralizing the heparin but its use is still in the experimental stage. Transfusions are also useful.

DR. GOLD: Cromer and Barker gave a single intravenous dose of menadione bisulfite (a synthetic vitamin K), 64 mg. (4 mg. per cc.) to a group of patients in whom dicumarol had produced excessive prolongation of the prothrombin time to such levels as eighty-five seconds or more, and fairly regularly obtained a prompt lowering of the prothrombin time. The result appeared in about two hours and reached a maximum in about eighteen hours. These doses of vitamin K are harmless.

DR. WRIGHT: The risk of hemorrhage in these patients is very slight, if the prothrombin time is accurately tested and the daily dose of dicumarol is withheld until the prothrombin level for that day is known. We have treated, or supervised the treatment with anticoagulants of more than 800 patients. We have had people die of carcinoma or progressive thrombophlebitis migrans but we have not had, so far, a single patient die of hemorrhage from dicumarol. In the recently operated surgical case, of course, the risk is greater. It is customary at the Mayo Clinic to start dicumarol therapy on the second or third day postoperatively in order to lessen the danger of hemorrhage.

VISITOR: How long do you continue the dicumarol after the patient is ambulatory?

DR. WRIGHT: We continue the patients on anticoagulant therapy after we get them up and about. We may keep them ambulant in the hospital for an extra week or ten days. It is like having a bear by the tail. We do not know exactly when to let go.

VISITOR: Is the treatment with dicumarol stopped abruptly?

DR. WRIGHT: We usually find it desirable to taper the dosage down gradually over several days. With an intelligent and cooperative patient it is sometimes possible to continue the dicumarol with the patient ambulant outside the hospital, having him go to a laboratory for tests of the prothrombin time.

DR. JANET TRAVELL: How often are these patients checked and how much dicumarol do they receive?

DR. WRIGHT: Most of our present ambulatory patients receive approximately 600 mg. a week in doses of 100 mg. daily; the dose is omitted on Sunday. That seems to be adequate for most patients. Whenever possible we have the prothrombin time checked daily or every other day and, of course, the dose is omitted on any day when the prothrombin activity is below 15 per cent of the normal.

DR. ANDRUS: How predictable is the effect of a given dose of dicumarol in a given individual?

DR. WRIGHT: In general, I believe that after a patient receiving dicumarol has been under observation for a period of two or three weeks, one learns enough about that patient to predict fairly accurately what the effect of a dose will be. However, the susceptibility of individuals varies greatly and it is unsafe to predict the effect of a dose at the start of therapy. Every once in a while an article appears recommending 1,000 mg. of dicumarol as the first dose. Such dosage is extremely dangerous. One may give 300 mg. as the first dose relatively safely, and 300 mg. on the second day, then tapering off gradually to 200 mg., and 100 mg. daily. If that dosage system is accompanied by a careful daily check of the prothrombin time, I do not think one will get into trouble very frequently but one may anticipate some minor hemorrhages.

Before we close this discussion I think I should say a word about the care of the patient after he recovers from the acute thrombophlebitis. Such care is one of the most important, but also one of the most neglected, phases of the management of this disease. We must remember that thrombophlebitis can be arrested but it should never be regarded as cured. Most of these patients have pains when they stand a long time and when the barometer changes. They worry about these pains and many of them become psychoneurotic because they never know whether the pain presages another attack of phlebitis. The neglect of proper prophylactic care increases the tendency of edema, ulcers and varicose veins. We can prevent these unfortunate sequelae by several means. It was found that a group of patients wearing knee length, well made, individually fitted elastic stockings for the first year after their thrombophlebitis had at the end of five years far less edema, far fewer pains and far fewer ulcers of the legs than those patients who went without stockings. I think that the use of such stockings is very important. It is essential to instruct the patient on how to prevent dermatophytosis. It is also most necessary to explain to the patient that pains in the legs do not always mean a recurrence of the thrombophlebitis. Fear of a recurrence may be one of the most serious disabilities. We have seen patients who, five years after the attack, are fearful of moving about or unnecessarily restrict their activities because they fear that when they have a pain in their leg they are on their way to a recurrence. This reaction is understandable in people who have passed through two or three attacks. We have formulated some arbitrary rules which have proved helpful to these patients. If the pain lasts less than an hour they should ignore it, for most of these pains last less than fifteen minutes. If it lasts one to three hours, they should lie down and elevate the feet or get into a tub of cool water, which frequently gives relief. If it lasts more than three hours, they should call their physician. Most of them will say, "Well, now that I know I don't have to worry about pain that lasts less than an hour, I go ahead and do what I want to do and have stopped worrying about it." There is the fact that some pains may recur for several years after an acute attack, and the patient's failure to understand this may result in much needless physical and psychoneurotic invalidism.

SUMMARY

DR. LAWRENCE W. HANLON: Some of the problems of treatment of thrombophlebitis were explored this afternoon. There are many varieties of thrombophlebitis differing in their causes, clinical aspects and pathologic changes. The regimen of treatment should be adjusted to the special requirements of the particular patient. The differentiation between phlebothrombosis and thrombophlebitis has limited value, since after a time, the thrombi in the two become pathologically indistinguishable. While thrombophlebitis often makes its appearance with characteristic signs and symptoms, such as pain, tenderness, swelling, fever and elevated sedimentation time in many of these patients the onset is silent and the first indication of the disease is a pulmonary embolus. Emphasis was placed on the desirability of making routine systematic examinations of the legs in surgical and non-surgical patients confined to bed, as a means of uncovering cases of thrombophlebitis sufficiently early to make it possible to prevent pulmonary complications.

The discussion covered measures that are useful in the prevention of thrombophlebitis, such as care against traumatization of vessels, prevention of infection, control of epidermophytosis, free movement in bed, early ambulation, deep respiratory exercises and the avoidance of the latter in thrombo-

phlebitis to prevent pulmonary embolism. Attention was called to the highly controversial nature of the measures used in the treatment of thrombophlebitis; the application of heat and cold, the use of leeches, prolonged rest, free exercise, early ambulation, dependent and elevated position of the extremity, lumbosacral sympathetic block, prophylactic venous ligation and the use of anticoagulant agents. It was indicated that the consensus favors hot, moist packs to the affected extremity, the elevated position of the limb to control swelling, a middle course in relation to rest and activity, the patient being allowed up and about after a short period of rest even though the disease is not fully checked provided anticoagulant therapy is employed. There are those who recommend prophylactic ligation of the veins in thrombophlebitis of the lower extremity in order to prevent embolism, although others prefer a more conservative course, ligating only after there is proof that the vein is a source of recurrent embolization. The choice of site for ligation depends on the location of the phlebitis.

The use of the anticoagulant agents, heparin and dicumarol, appears to be an advance of the first importance in the treatment of thrombophlebitis. Figures were cited showing most extraordinary results following their use; for example, second thrombosis or embolus was reduced from an incidence of nearly 50 per cent to about 1 per cent, cases of fatal pulmonary embolus with an incidence of nearly 6 per cent completely vanished. The discussion embraced the details of application, dosage, mode of action, dangers and methods of control of anticoagulant therapy.

Clinico-pathological Conference

Gastrointestinal Disease with Hematemeses and Hepatic Insufficiency*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a thirty-seven year old Negro Pullman porter who entered the Washington University Clinics on November 22, 1946, complaining of indigestion, nausea and vomiting. The family history was irrelevant. The patient had had Neisserian infection twice; both times he recovered uneventfully. He had an occasional hacking cough, productive of blood-streaked sputum, and stated that his gums bled easily, apparently because of poor dental hygiene. Although his diet seemed adequate, he took a moderately large amount of alcohol. There was no history of ingestion of drugs or contact with heavy metals.

He was quite well until seven months prior to his admission to the Clinic when he developed a sensation of fullness in the upper abdomen after meals, usually associated with considerable abdominal distention and especially noted after the ingestion of fatty pork. He usually vomited almost immediately after eating but occasionally one to one and one-half hours later. He consulted a physician who prescribed medication of an unknown type, and was then relieved until four weeks before entry when again after eating fatty meat, he developed abdominal distention, nausea and vomiting. Subsequently he had moderately severe burning distress in the upper abdomen occurring usually at night; it was relieved by milk but only questionably by alkalis. He vomited three to four times daily and four days before coming to the Clinic noted bright red blood in the vomitus. During the first and second episodes of abdominal pain, the patient thought his urine had become darker than usual. Five days before coming to the Clinic he developed generalized pruritus. Although he had felt feverish, he had not taken his temperature.

Examination in the Clinic revealed the vital signs to be normal. The patient was well nourished and well developed but appeared somewhat ill. The skin was dry but there was no apparent weight loss. The sclerae were icteric; the pupils reacted well to light and accommodation and the fundi showed only slight arteriolar narrowing. Examination of the mouth revealed marked pyorrhea. The tonsils were large and the pharynx red. The heart and lungs were normal. The liver edge was rounded and was felt 4 cm. below the right costal margin. The spleen could not be palpated. The prostate gland was normal and no neurologic findings of significance were described.

The laboratory studies were as follows: Blood count: red cells, 5,760,000; hemoglobin, 15.3 Gm.; white cells, 8,600; differential count: stab forms, 6 per cent;

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

segmented forms, 65 per cent; lymphocytes, 29 per cent. Urinalysis: albumin, very faint trace; bile, negative; sediment, negative. Stool: guaiac negative. Blood Kahn test: negative. Icteric index: 21. Hippuric acid test: 33 per cent excretion of sodium benzoate. Gastrointestinal roentgenograms: "The gastric motility is adequate. The duodenum shows a marked pressure narrowing of the proximal second portion with a fine longitudinal relief pattern not indicating an intrinsic but rather an extrinsic pressure deformity, apparently from the pancreas." Cholecystogram: "The gallbladder could not be visualized."

While the gastrointestinal x-rays were being made, the patient vomited about one-half cup of bright red blood, and on December 3, 1946, he was admitted to the hospital.

On admission, the only significant change in the physical examination from those previously recorded was the presence of a Grade II systolic murmur in the third and fourth interspaces. Laboratory studies included a red cell count of 3,560,000 with 13.5 Gm. of hemoglobin. The urine was positive for bile and urobilinogen was present in a dilution of 1:20 but not of 1:40. Other laboratory findings included the following: cephalin-cholesterol flocculation test: 3+; alkaline phosphatase, 12 Bodansky units; icteric index, 90; Van den Bergh test: direct, 4.5 mg. per cent; indirect, 2.3 mg. per cent; serum amylase, 112 units; cholesterol, 198 mg. per cent; prothrombin time, 75 per cent of normal; total proteins, 6.3 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 3.5 Gm. per cent.

On the day following admission the patient vomited 400 cc. of blood-streaked material. On examination at that time his abdomen was noted to be distended and tympanitic. Surgical consultation was obtained but no indication for operative intervention was apparent.

On the fifth hospital day urobilinogen was present in the urine in a dilution of 1:80. The urine continued to be positive for bile as did the stool. Although he continued to vomit blood-tinged material occasionally, the patient took a restricted diet quite well. On the eleventh hospital day a second gastrointestinal x-ray series again showed no intrinsic abnormality of the duodenum but the same extrinsic pressure defect as reported in the earlier films. Two and one-half weeks after admission to the hospital the patient's abdomen became more distended and signs of ascites became apparent.

Laboratory studies at this time were as follows: The urine was positive for bile and urobilinogen was present in a dilution of 1:60. The stool was likewise positive for bile. Total protein, 5.5 Gm. per cent; albumin, 2.2 Gm. per cent; globulin, 3.3 Gm. per cent. Icteric index, 70. Van den Bergh test: direct, 4.5 mg. per cent; indirect, 2.27 mg. per cent. Cephalin-cholesterol flocculation test: 4+. Alkaline phosphatase: 12 Bodansky units.

On the twentieth hospital day the patient complained of sharp cramping pain in the mid-abdomen and epigastrium which was relieved somewhat by atropine. Shortly thereafter, he began to hiccough, and vomiting, which had subsided, recurred with production of a small amount of clear yellowish fluid. The temperature was 38.6°c., pulse 100, respirations 36, and blood pressure 120/70. The abdomen was markedly distended and tympanitic and there was dullness in the flanks. Although moderate tenderness was noted in the upper portion, there was no true spasm. A paracentesis was performed and 1,200 cc. of greenish-yellow fluid were removed. The specific gravity was 1.010 and there were 108 cells of which 90 per cent were mononuclear forms. The protein content of the ascitic fluid was 0.7 Gm. per cent. On culture the fluid was sterile. The red blood

count at this time was 5,000,000, the white count 7,900, and there was a slight left shift in the differential count.

The patient was again seen by a surgical consultant but it was not believed that operation was indicated. A Levine tube was passed and 150 cc. of brownish, thick fluid was obtained. Wangensteen suction was instituted but abdominal distention was not relieved. Because of the persistent elevation of the temperature and pulse, penicillin was begun in dosages of 40,000 units every three hours intramuscularly.

On the day following onset of abdominal pain the white count rose to 14,000 with 6 per cent juvenile forms and 80 per cent stab forms in the differential count. The icteric index was 80 and the non-protein nitrogen 25 mg. per cent. The patient was weaker and his abdomen remained distended. He complained of occasional sharp stabbing mid-abdominal epigastric pain. The temperature was again 38.6°c., the pulse 120, but the blood pressure had fallen to 90/60. An x-ray film of the abdomen was described as showing distention of the small bowel and questionable air beneath both diaphragms. The blood amylase on this occasion was 370 units per cent. A second paracentesis was performed three days after the first and 500 cc. of cloudy orange-yellow fluid were removed. The specific gravity was 1.014, the protein content 2.5 Gm. per cent, and there were 8,000 cells of which 55 per cent were polymorphonuclear forms. On culture coliform organisms were recovered. Streptomycin was given in dosages of 0.25 Gm. every three hours intramuscularly. On the day following the second paracentesis the patient's temperature was 38.4°c., pulse 130, respirations 24, and the blood pressure 90/70. He was unresponsive to questions; the heart sounds were of good quality and signs of bilateral pleural effusion, thought to be due to the high diaphragms, appeared. During the course of the day the peripheral pulsations were no longer palpable and although the heart sounds continued to be of good quality, the blood pressure fell to 50/0. The extremities became cool. Following the infusion of two units of plasma the pulse rate was 134, respirations 34, and blood pressure 72/50. The patient continued to do poorly despite supportive therapy and his temperature rose to 39.2°c. He expired on December 27, 1946. During his hospital stay he received large amounts of choline, vitamins, and intrahepatol.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Seven months before his death this thirty-seven year old Pullman porter first had an episode of abdominal distress associated with nausea and vomiting. Within a few days he felt well and not until six months later did symptoms of gastrointestinal disease reappear. The second episode was characterized by abdominal distention, vomiting and burning epigastric distress. It would be well to inquire what lesion might produce such symptoms. Dr. Duden, would you comment on this point?

DR. CHARLES N. DUDEN: I saw this patient in the Clinic and subsequently in the hospital. At first, we were very puzzled as to the nature of the disease and when he was admitted to the hospital, we had made no specific diagnosis. Since the original discomfort apparently followed indiscretion in diet, and in view of the fact that the patient had an alcoholic history, it was believed that the entire symptom complex might have arisen as a result of his poor eating habits. Early Laennec's cirrhosis was considered, as was gallbladder disease, although it was believed that the patient was young for the latter.

DR. ALEXANDER: In other words, you considered that the vomiting originally may not have been due to an obstructive

lesion but rather that it may have been a reflection of cholecystitis or cirrhosis. Dr. Scheff, what is your feeling regarding the nature of this patient's illness?

DR. HAROLD SCHEFF: In my opinion, the two most likely possibilities are gallbladder disease and peptic ulcer. The burning pain, coming on often at night and relieved by milk, certainly suggests the pain of peptic ulcer. I agree with Dr. Duden, however, that the patient had signs of Laennec's cirrhosis.

DR. ALEXANDER: He certainly had evidence of liver damage, particularly later in his course. When you spoke of gallbladder disease, were you referring to cholecystitis?

DR. SCHEFF: Yes, I meant to imply inflammation of the gallbladder associated with biliary calculi. Since the patient was jaundiced, a calculus was probably in the common bile duct.

DR. ALEXANDER: Would you entertain the idea that esophageal varices, secondary to cirrhosis, gave rise to the hematemeses?

DR. SCHEFF: Yes, that is possible, but from the *x*-ray studies we know that there was an abnormality of the second part of the duodenum, and I have seen similar roentgenologic changes produced by an ulcer in that region.

DR. ALEXANDER: On two occasions, however, the radiologists interpreted the films as showing an extrinsic lesion. Dr. Bottom, do you think that an ulcer in the second portion of the duodenum could have given rise to the x-ray findings?

DR. DONALD S. BOTTOM: I think that very unlikely.

DR. ALEXANDER: May there have been an ulcer of the first portion of the duodenum?

DR. BOTTOM: Possibly.

DR. BRUCE D. KENAMORE: I believe compression of the second portion of the duodenum, as indicated by the roentgenograms, could have been responsible for all of the patient's symptoms. Extrinsic pressure may occasionally produce hemorrhage by causing tension and rupture of the vessels within the duodenal wall.

DR. ALEXANDER: You are not attracted to the possibility that the patient had a duodenal ulcer?

DR. KENAMORE: No, I am not. I believe that he may have had a secondary erosion but that peptic ulcer was not the primary lesion.

DR. ALEXANDER: Are there other suggestions?

DR. JOHN. R. SMITH: Those of us who saw the patient after his admission to the hospital considered duodenal ulcer as a very likely possibility. The question was raised as to whether the ulcer might not have perforated into the pancreas, giving rise to an inflammatory process which caused partial obstruction of the common bile duct and possibly of the pancreatic duct. The latter thought prompted the determination of the serum amylase.

DR. ALEXANDER: If the constriction of the duodenum was extrinsic, what lesion might be responsible?

DR. SMITH: One should consider the possibility of an annular pancreas.

DR. ALEXANDER: Is not such a lesion very rare?

DR. SMITH: I do not know the exact figures but it certainly does not occur very often.

DR. ALEXANDER: I believe Lehman assembled only forty-three cases in all of his study. Dr. Moore, how often have you seen an annular pancreas?

DR. ROBERT A. MOORE: I have seen only one.

DR. ALEXANDER: In annular lesions of the duodenum, are there symptoms other than those due to the obstruction?

DR. DUDEN: No, I do not believe so. I also am of the opinion that a duodenal ulcer was not the primary lesion. Another

possibility is a congenital deformity of the duodenum with subsequent development of an ulcer. A large cirrhotic liver or an enlarged gallbladder might have given rise to the roentgenologic findings, and conceivably a tumor at the head of the pancreas could likewise have done so.

DR. ALEXANDER: Dr. Wade, would you comment on the possibility of liver disease? Do you think the liver was seriously compromised?

DR. LEO J. WADE: I considered the possibility that the liver could have been responsible for the obstruction. However, it is stated that the liver extended only 4 cm. below the costal margin. The possibility of a carcinoma in the liver also must be considered.

DR. ALEXANDER: You are assuming that the patient had underlying cirrhosis?

DR. WADE: Yes. I think the original symptoms seven months prior to entry may have been due to cirrhosis.

DR. ALEXANDER: Subsequently, the patient developed evidence of significant liver dysfunction as indicated by results of the cephalin-cholesterol flocculation test, the high serum globulin and the decreased prothrombin time. The urine urobilinogen also rose.

DR. WADE: The increase in urine urobilinogen, I believe, indicates definite hepatic disease.

DR. GUSTAVE J. DAMMIN: I agree that the increasing urine urobilinogen suggests impairment of liver function.

DR. ALEXANDER: How may the distinction between cirrhosis and hepatitis in a situation such as this be made? The patient was jaundiced before his terminal illness; may a similar clinical picture arise in acute hepatitis?

DR. WADE: Yes, I think that it might. I prefer, however, to link all of the patient's symptoms in the course of the last seven months together and that could be done better with a diagnosis of cirrhosis.

DR. ALEXANDER: On the other hand, as far as the clinical history goes, there was no continuity of symptoms. The patient had a brief episode and was then quite well for six months. Nevertheless, your point is well taken.

DR. WADE: The red count of 3,500,000 would be more compatible with cirrhosis than with uncomplicated acute hepatitis but in the presence of hematemeses the anemia cannot be used *per se* to support the diagnosis of cirrhosis.

DR. SCHEFF: I would like to ask Dr. Wade how frequently advanced cirrhosis is seen in a patient of this age.

DR. WADE: It is true that the incidence of cirrhosis increases with advancing age and is most marked in the fifth and sixth decades, but advanced cirrhosis may be seen in fairly young people and it is occasionally seen even in young children.

DR. WILLIAM H. OLMSTED: The size of the liver as described seems small for carcinoma.

DR. WADE: The liver need not be enlarged for carcinomatous change may be quite localized.

DR. ALEXANDER: In the presence of cirrhosis how frequently is the gallbladder normal?

DR. SCHEFF: In my experience gallbladder disease occurs quite frequently in patients with cirrhosis.

DR. ALEXANDER: Although the primary diagnosis remained a problem, the patient suddenly developed signs pointing to a change in the status of the abdominal lesion. His temperature and white count rose and the differential count shifted to the left. These changes occurred before the first paracentesis. There was a suggestion of air under the diaphragms and some indication of peritonitis. Dr. Kenamore, do you believe that rupture of a viscus occurred?

DR. KENAMORE: Yes, I do.

DR. PALMER H. FUTCHER: I am not sure that I agree that either rupture of a viscus or peritonitis existed. The coliform organisms conceivably could have been contaminants. I believe thrombosis of the portal vein must be considered, for it can produce symptoms very similar to those observed in this case.

DR. ALEXANDER: If there was peritonitis due to a coliform organism, might the organisms themselves form enough gas to be visible roentgenologically?

DR. CARL G. HARFORD: I do not think so.

DR. SAMUEL C. BUKANTZ: The patient's acute episode with pain developed before the first paracentesis and the air under the diaphragms was noted after the paracentesis. How often may air be seen under the diaphragm following paracentesis?

DR. ALEXANDER: Your point is a good one for paracentesis may lead to air under the diaphragm frequently. However, the presence of coliform organisms suggests the likelihood of peritonitis which certainly may have arisen as a result of perforation.

DR. OLMSTED: I believe that pancreatitis should be mentioned.

DR. ALEXANDER: Yes, pancreatitis could have explained the pain and it is true that the serum amylase rose. It was suggested earlier that the patient may have had an ulcer of the duodenum which ruptured into the pancreas giving rise to pancreatitis with the associated high amylase.

DR. DUDEN: I should like to mention a case recently seen in which marked constriction of the duodenum seemed apparent from roentgenologic studies. A diagnosis of annular pancreas was made and the patient was explored. At operation no cause for the narrowing was found. It must be emphasized that narrowing such as was seen here may occur without extrinsic pressure.

DR. ALEXANDER: It is apparent that no general agreement can be reached on the primary diagnosis or the cause of death in this case. Considerable opinion favors cirrhosis of the liver. It is possible that the patient had a duodenal ulcer with rupture either into the peritoneal cavity or into the pancreas; if the latter occurred, pancreatitis resulted. It seems likely that the patient had peritonitis due to a coliform organism, but it is possible that the terminal abdominal symptoms were due to thrombosis of the portal vein and that the air under the diaphragm arose as a result of the paracentesis.

Clinical Diagnosis: ?Laennec's cirrhosis; ?duodenal ulcer with rupture into the peritoneal cavity or the pancreas with resultant pancreatitis; peritonitis due to coliform organisms.

PATHOLOGIC DISCUSSION

DR. BETTY B. GEREN: At autopsy the body was that of a well developed, well nourished Negro male. The sclerae were markedly icteric and there was generalized enlargement of the superficial lymph nodes. On opening the thorax, petechiae and focal hemorrhages were found beneath the pleurae of the lungs and there was massive atelectasis of the lower lobes of both lungs and focal atelectasis of the other lobes. In the right pleural cavity there were 200 cc. of yellowish, blood-tinged fluid and 150 cc. of similar fluid were present in the left pleural cavity. Aside from petechiae beneath the epicardium, the heart was not remarkable. When the abdomen was opened, large numbers of gas bubbles were seen and the peritoneal cavity contained 4,500 cc. of bile-stained fluid. The liver weighed 1,100 Gm.; its surface was finely nodular, the nodules being yellowish and averaging 3 to 6 mm. in diameter. They were elevated 1 to 2 mm. above the intervening, firm, pinkish, fibrous tissue. The capsule was slightly thickened. On section similar yellowish nodules were seen, in marked contrast to

the firm, retracted, pinkish tissue in the widened portal spaces. Greenish pigmentation was seen in some of the portal spaces. The spleen weighed 160 Gm. and was markedly congested. In the esophagus, 11 cm. proximal to the cardia, there was a 1.5 by 1.0 cm. erosion of the mucosa but no varices were found. At the level of the cardia a 3.5 by 1.5 by 1.0 cm. irregular, firm, white tumor mass was present in the submucosa. The rugae of the stomach were markedly prominent and there was a large amount of mucus on the surface of the gastric mucosa. In addition, a small amount of granular material was present in the lumen and there were petechiae and focal hemorrhages in the mucosa of the fundus of the stomach. On the serosal surface of the first portion of the duodenum, 1 cm. distal to the pylorus, there was a 4 mm. perforation of the anterior wall. The ulceration involved all layers of the wall of the duodenum and measured 1.0 by 0.5 cm. on the mucosal surface. On the posterior wall of the duodenum there was an ulceration of the mucosa and submucosa, measuring 6 mm. in greatest diameter, which did not involve the muscularis or deeper layers. All of the peritoneal surfaces were covered with a yellowish-white exudate.

DR. MOORE: It is apparent that this patient had two major diseases. First, he had two duodenal ulcers in the first portion of the duodenum, 1 cm. and ½ cm. from the pylorus, respectively, the closer one of which, lying anteriorly, had perforated through the entire thickness of the duodenum into the free peritoneal cavity. The ulcer on the posterior surface was superficial and extended only through the submucosa. Although headed in that direction, it had not reached the pancreas, and there was no evidence of pathologic change in that organ immediately below the ulcer. Second, the patient had cirrhosis of the liver of moderately advanced degree associated with slight to moderate portal hypertension as evidenced by ascites. At autopsy there was no evidence, however, of chronic passive congestion of the portal system. The spleen weighed only 160 Gm., and although it was congested, the congestion may have been associated with the peritonitis rather than with long standing portal hypertension. The gastrointestinal mucosa did not show the degree of chronic passive congestion that would have been expected if cirrhosis of the liver had been responsible for marked portal hypertension. There were no pathologic changes in the gallbladder to account for the fact that it was not visible when cholecystography was performed. Dr. Duden's statement that the second portion of the duodenum may show apparent extrinsic pressure when no lesion involving that area could be found is borne out by the fact that in this case, no pathologic process involving the second part of the duodenum could be identified.

The microscopic sections are interesting in regard to the duration and nature of the lesions involving the duodenum and the liver. The first section (Fig. 1) is a striking example of a perforated ulcer at the point of perforation. It shows the mucosa of the duodenum on both sides, the base of the ulcer with the overhanging edge of slightly hyperplastic mucosa and the defect in the wall. The lower half of the slide represents the free peritoneal cavity. If one examines the tissue carefully, evidence of the age of the ulcer may be obtained. Figure 2 is from the peritoneal surface of the ulcer bed and shows the muscularis and the peritoneum. The latter is thickened by proliferation of connective tissue which is moderately mature. It still contains a goodly number of capillary vessels but the thickening is significant. Such changes cannot occur in less than weeks or possibly months. It is seen that the base of the ulcer is completely devoid of muscular tissue. No necrosis is

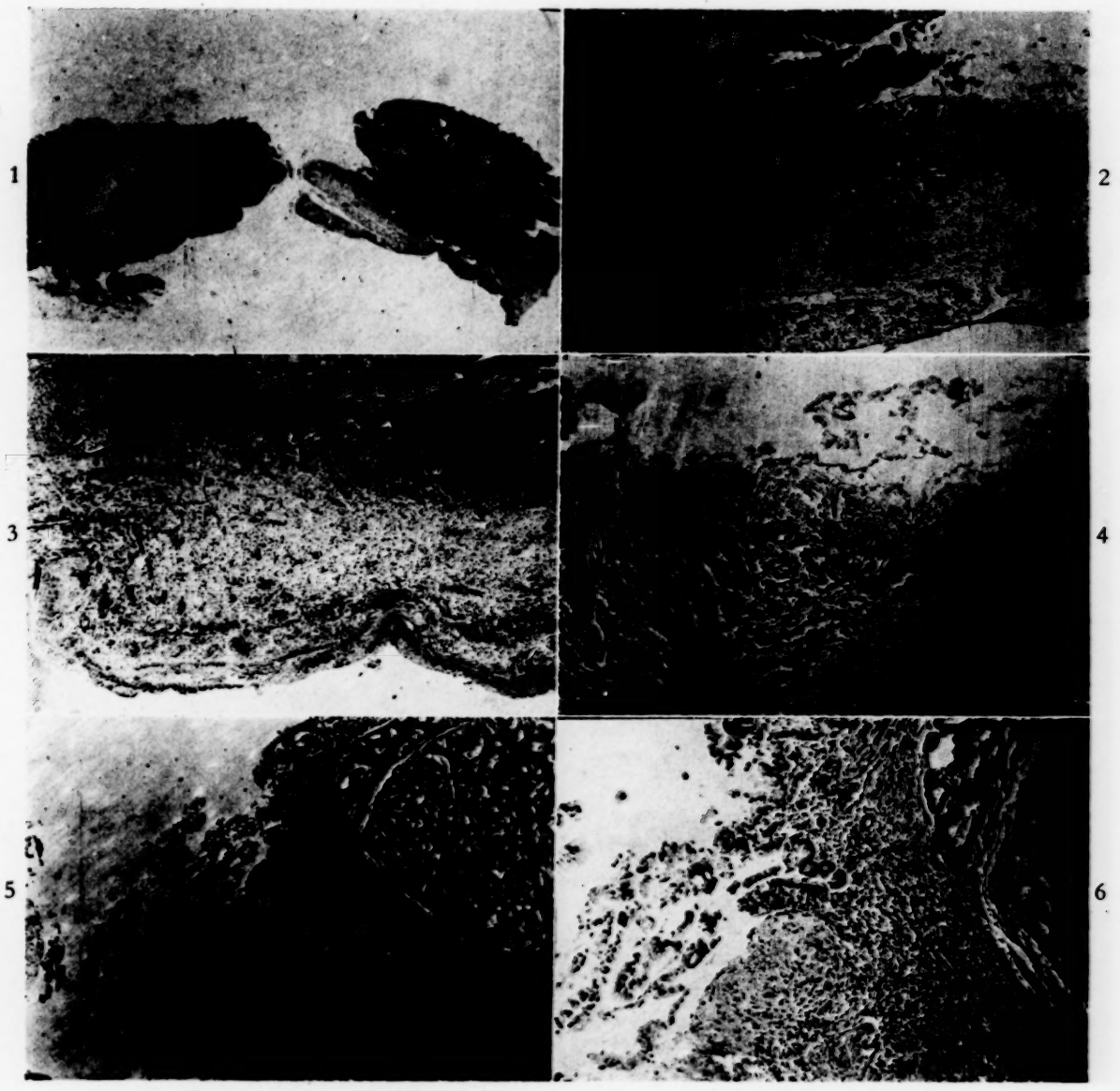


FIG. 1. Low power photomicrograph at the site of the perforated ulcer.
FIG. 2. Section showing the peritoneal surface of the ulcer bed in the region of the perforation.
FIG. 3. Section of the peritoneum showing changes indicating a chronic ulcer.
FIG. 4. Section through the bed of the ulcer showing layers of necrosis, granulation tissue and collagen.
FIG. 5. Section at the edge of the ulcer with epithelium on its surface.
FIG. 6. High power view of Figure 5.

evident in the muscle at the point of perforation, again indicating that the perforation occurred some time before death. In other words, there was an attempt at repair which is seen in a chronic or subacute peptic ulcer. Figure 3 shows the peritoneum in another area. There is again great thickening, indicative of chronicity as far as the ulcer is concerned. In Figure 4 the bed of the ulcer is seen with the characteristic three layers previously described, namely, the superficial layer of necrosis, a layer of granulation tissue and far beneath a layer of collagen in which the granulation tissue has undergone maturation. The formation of collagenous granulation tissue is another

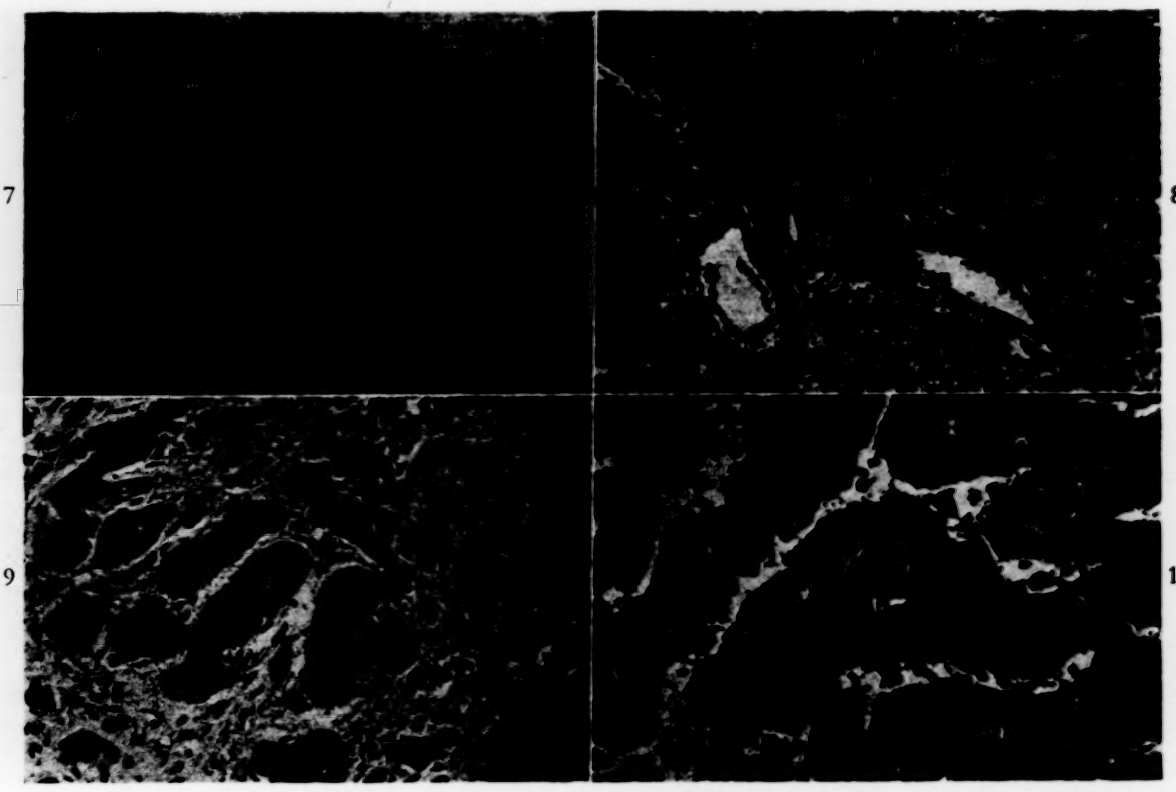


FIG. 7. Section showing the changes of peritonitis.
FIG. 8. Section of the liver illustrating the process of cirrhosis.
FIG. 9. Section from the liver showing two columns of liver cells separated by a bile duct.
FIG. 10. Another section from the liver, under higher magnification, showing intrahepatic obstruction with distention of bile canaliculi.

indication of chronicity of an ulcer. The thick layer of necrotic tissue also indicates activity. Further evidence in regard to the age of the ulcer is seen in Figure 5, showing epithelium on the surface of the edge of the ulcer which may have been desquamated from that surface. If the surface was covered by epithelium, it was a healing peptic ulcer and suggests that the patient may have had a period of activity following which there was healing and then, a week or so before death, new activity and a new erosion occurred. Figure 6 shows a higher power view of the edge of the ulcer with the single layered epithelium which may have been desquamated from the edge. I believe that it was most probable that the ulcer was healing and that activity occurred shortly before death and led to perforation. In Figure 7 the peritonitis is seen. There is a fibrinoserous and slightly cellular exudate indicating an acute lesion.

Considering the liver, in Figure 8 a portal space is seen showing recent connective tissue, cellular infiltration and isolation of individual liver cells throughout the connective tissue. This process indicates fairly active cirrhosis of the type in which there has been widespread destruction of the liver and regeneration of both lobules as well as of individual groups of liver cells out in the connective tissue. It is the type of change that twenty years ago would have been called "toxic cirrhosis of the liver"; today, we are not clear as to the exact origin of the process, for it may come from a number of initiating lesions.

In regard to the problem of where regenerating liver cells arise, that is, whether from other liver cells or from bile ducts, it is

of interest to examine Figure 9. A small bile duct is seen between two columns of liver cells. This finding might be interpreted as indicating that the liver cells are actually arising from the bile duct but such an interpretation is only a postulation and not a statement of proven fact.

Figure 10 shows the reason for the patient's jaundice. There is intrahepatic obstruction and the intercellular bile canaliculi are distended with bile and in certain areas, so-called bile thrombi have been formed by dilatation of the intercellular bile canaliculi.

Summarizing then, it can be said that the patient probably had a peptic ulcer for some time, possibly healing until a short time before death when it became reactivated leading to perforation and peritonitis. There was also active cirrhosis of the liver, possibly toxic in type. Since in the clinical discussion Dr. Alexander brought up the question of infectious hepatitis, it will be of interest to present three current views concerning the relation of infectious hepatitis to cirrhosis of the liver. I shall quote significant statements from each of three important papers recently published. First of all, a paper by Balduin Lucké,[1] summarizing the Army material: "In the present investigation there was found no evidence of permanent damage to the hepatic parenchyma and restoration of the liver was practically complete." The next selection is from the experience of Dible[2] in England: "That acute and subacute necrosis and cirrhosis could follow epidemic hepatitis has been recognized previously. Our studies further emphasize this sequence." Wood,[3] reporting the work in the United States Navy, said: "There is lack of agreement among pathologists as to whether or not cirrhosis may result and if it does, whether it is of the so-called toxic or portal type." Whether or not this man had epidemic hepatitis as a forerunner of his cirrhosis, I do not know.

Dr. Alexander: The esophageal lesion was of no significance?

Dr. Moore: It was a leiomyoma and clinically insignificant. The esophageal ulcer was a terminal one in a person who had vomited a great deal.

Pathologic Diagnosis: Subacute and chronic peptic ulcers of the duodenum with perforation of one; serofibrinous peritonitis, generalized (4,500 cc. bile stained fluids and large amounts of gas in peritoneal cavity; Escherichia coli cultured from ascitic fluid and blood stream at autopsy); atelectasis of the lungs, massive of the lower lobes, and focal of the nodular cirrhosis, advanced.

[1] Lucké, B. Structure of liver after recovery from epidemic hepatitis. *Am. J. Path.*, 20: 595–619, 1944.

[2] Dible, J. H., McMichael, J. and Sherlock, S. P. V. Pathology of acute hepatitis; aspiration biopsy studies of epidemic, arsenotherapy and serum aundice. *Lancet*, 2: 402–408, 1943.

[3] Wood, David. Further notes on the pathology of acute epidemic hepatitis and hemologous serum jaundice. *Am. J. Clin. Path.*, 16: 746–751, 1946.

Case Reports

False Positive Biologic Tests in Lymphogranuloma Venereum*

GASTON E. BLOM, M.D.
NEW YORK, NEW YORK

As a result of the advances in the separation of human blood protein into several fractions,[1] an increasing number of biological phenomena are being attributed to the globulin components of plasma. Fractions in the normal globulin partition or in hyperglobulinemia appear to be responsible factors in a number of laboratory tests which have not previously been well understood. These include the Wassermann reaction,[2] cephalin-cholesterol flocculation and colloidal gold tests,[3,4] Takata-Ara reaction[5] and formol gel test.

Lymphogranuloma venereum is a disease in which hyperglobulinemia is a common finding.[5,6,7,8,9,10,23] Though Mann[10] reports this to be particularly true of the chronic phase of the disease in which the globulin may be permanently elevated, Kampmeier, Smith and Larsen[9] report its presence in sixty-two out of sixty-seven patients in early stages. In a series of seventy-nine patients Jones and Rome[5] found the globulin concentration to be greater than 3 Gm. per cent in 95 per cent, with significant and rapid variations occurring over a short period of time. One might expect therefore in this disease a high incidence of false positive laboratory tests which are attributed to a high globulin concentration. Clinical reports of such phenomena are surprisingly few and those which do exist are largely concerned with false positive serologic and anticomplementary Wassermann reactions. Jeghers and Selesnick[11] found that hyperproteinemia especially in lymphogranuloma venereum and multiple myeloma gives rise to anticomplementary Wassermann reactions. Stokes[12] and others report the anticomplementary reaction as being common in lymphogranuloma. Johnson and Burnet[7] state false positive serologies are found in 5 to 10 per cent of cases of lymphogranuloma while Koteen[13] states the incidence is as high as 33 per cent. The true incidence of these reactions is difficult to ascertain largely because of the transitory nature of the Wassermann reaction. Jones and Rome[5] reported a high incidence of positive Takata-Ara reactions in ninety-nine cases of lymphogranuloma venereum. Of this number, fifty had positive reactions with no evidence of disturbance in liver function as indicated by the bromsulfalein, the urine urobilinogen, the van den Bergh and the galactose tolerance tests. Forty-seven of the fifty cases had associated elevation in globulin.

It is rare that one has the opportunity to study lymphogranuloma venereum in the early stages, which may explain the variable clinical reports on false laboratory tests. The following case is therefore reported.

CASE REPORT

L. L. was a forty-three year old male Negro who was admitted to the Presbyterian Hospital with a painful swelling in the left groin of three weeks' duration. The patient acknowledged

* From the Department of Medicine of the College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York. Present Address; U. S. Public Health Service Hospital, Fort Worth, Texas.

LABORATORY DATA

Date	E.S.R. *	Total Serum Protein†	Serum Globulin†	Cephalin Flocculation	Heterophile Agglutination	Serology	Miscellaneous
1-5-45		7.2	3.2			Kline 0 Wassermann 0	
1-8-45	80						Temperature 105.4°F. WBC 12,650
1-9-45		7.9	4.4	+++		Kline 0	Cold agglutination 1:32
1-11-45	93						WBC 6,900
1-12-45					1:128		Temperature normal
1-15-45	108			+++		Kline 0 Wassermann Alcoholic ++++ Cholesterol ++++	
1-16-45		7.7	4.3				WBC 9,850
1-19-45	62						Frei test ++
1-21-45		Discharged					Frei test (autoantigen) ++
1-30-45	27	7.7	3.2	+	1:32	Kline 0 Wassermann 0	Cold agglutination 0
2-6-45	14	7.5	3.0	0	1:16		
2-20-45					1:32		

* Sedimentation rate in mm/hr. Normal maximum 15 mm.
† Values given in Gm. per cent.

having had sexual intercourse four weeks before the onset of his first symptoms. Though he did not notice a herpetic penile sore, his symptoms of low backache began four weeks prior to admission. Three weeks prior to admission he developed a small, painful, marble-sized lump in his left groin which slowly increased to the size of a walnut and one week prior to admission he developed headache, chills, fever and malaise. Upon admission he had a temperature of 105°F. (p.r.) but because of its subsequent subsidence to 99.8°F. (p.r.) in forty-eight hours he was allowed to return home. Two days later he returned to the hospital with the same symptoms.

The patient's temperature was 105.4°F. (p.r.), pulse 100, blood pressure 122/72.

On second admission to the hospital the patient was an acutely ill but well developed and well nourished Negro male. His sclerae and conjunctivae were injected and there was a loud blowing systolic murmur heard in the mitral area. In the left groin there was a fusiform swelling 2 by 5 cm. with no heat and redness but deeply fluctuant and somewhat tender.

The above laboratory data in tabular form indicate the changes that occurred in the patient's hospital course. Additional data not included are: negative bubo pus and blood cultures, hemoglobin 13.6 Gm., red blood count 4.70 million. Repeated blood smears were negative for infectious mononucleosis cells.

The patient was given sulfathiazole in the dose of 2 Gm. initially and 1 Gm. every six hours. With drug levels of 3 mg. per cent there was a dramatic drop in temperature and a marked disappearance of the constitutional symptoms within forty-eight hours.

The patient was discharged on the thirteenth hospital day on a maintenance dose of sulfathiazole of ½ Gm. three times daily. He was followed in the out-patient department weekly for one month. Two weeks after discharge chemotherapy was discontinued and the patient remained asymptomatic. At the time of the last clinic visit the laboratory data had reverted to normal.

COMMENT

The clinical response to chemotherapy would appear to be more dramatic than what one would normally expect. Noojin et al.,[14] however, reported ten cases of lymphogranuloma venereum treated with either sulfathiazole or sulfadiazine, with all patients afebrile in twenty-four hours. The

dose used was larger than that employed here, i.e., 6 Gm. the first day and 3 Gm. daily for twenty days.

In addition to the laboratory data recorded, attempts were made to prove the existence of the lymphogranuloma virus in bubo pus by animal transmission experiments and the preparation of an antigen.

Bubo pus was aspirated on the second hospital day. This cultured negative, and on smear contained a predominance of mononuclear cells. An antigen was prepared after the method first described by Frei[15] in 1925 in which the bubo pus is diluted five times with normal saline, and sterilized by heating to 60°C. two hours the first day and one hour the second day. The material is tested for sterility and stored in a refrigerator.

This antigen was employed as skin test material not only on this patient but on other known Frei-positive individuals. In four patients known to have positive Frei tests* and one with the clinical manifestations of lymphogranuloma venereum, this antigen produced a positive skin test in every case. In four known normal Frei-negative patients* this preparation gave a negative reaction.

An attempt was made to transmit the viral agent in the bubo pus to yolk sacs of the chick embryo and mouse brain. Injection of the bubo material into the yolk sacs of chicken embryo produced no growth. Several white mice were injected intracerebrally with diluted bubo material. None of the animals developed characteristic signs of cerebral involvement (humped back, ruffled hair, tremors, ataxia, paralysis and convulsions). However, the use of sulfathiazole previous to aspiration of the bubo may have sufficiently reduced the virulence of the virus. Callomon and Brown[16] found the virus present in the brains of mice injected intracerebrally and treated with sulfonamides. Though the animals did not show any clinical evidence of infection, pathological material showed characteristic cellular changes in the brain substance.

In the case reported a significant increase in globulin concentration was noted during the active virus infection. This increase occurred over a relatively short period of time and it was during this period that four serological tests became positive, a phenomenon more commonly associated with other infections. It is doubtful whether this can be attributed solely to an increase in globulin, and therefore altered globulin (s) is suggested as the basis for some of these reactions. These four serological tests are discussed below.

The cephalin-cholesterol flocculation test is closely related to disturbances in the protein partition.[22] Hanger et al.[3,4] have demonstrated that gamma globulin is the sole component of serum protein giving a positive cephalin flocculation and that a positive reaction can be expected when an increase in gamma globulin is not sufficiently inhibited by serum albumin. In the case reported the return of the cephalin flocculation to normal from three plus was coincident with the return of elevated globulin to a normal range.

Cold agglutination is considered by most workers to be a non-specific response to infection. Though this phenomenon occurs most commonly in primary atypical pneumonia,[17,18,19] it is present in a variety of other diseases,[18,20] particularly those of viral origin. Cold agglutinins are probably present in the globulin fraction of plasma. A titer of 1:32 in this case was considered significant in that it returned to zero when the infection was no longer active.

The heterophilic antibody reaction is considered specific for infectious mononucleosis but increases in titer have been found in pneumonia, measles, tuberculosis, scarlet fever, filariasis, aplastic anemia and

* Previously tested with commercial yolk sac antigen.

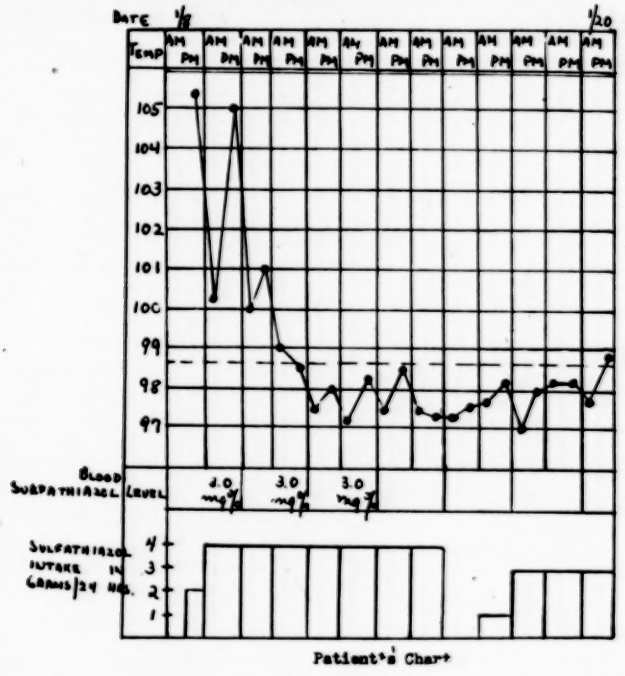


FIG. 1.

leukemia. Actually, the highest titers have been found in diseases other than infectious mononucleosis.[21] The heterophilic antibody probably lies in the globulin fraction of plasma. Hyperglobulinemia does not appear to be associated with the Paul-Bunnell reaction and so the reversion of a titer of 1:128 to a normal range of 1:32 in this case should be attributed to the disappearance of the antibody as the infection became inactive.

Hyperglobulinemia is associated with anticomplementary Wassermann reactions while the true Wassermann reaction is due to a specific antibody. By electrophoretic studies[2] the Wassermann antibody has been found in the globulin fraction between beta and gamma globulins. There appears to be no difference between false positive and true positive Wassermann sera. An altered globulin presumably caused the transitory positive Wassermann recorded in the case reported.

Evidence indicates that these four serological tests (cold agglutination, cephalin flocculation, Wassermann reaction and heterophile agglutination) lack specificity and that the basis for them is a disturbance in the globulin fraction. The table given below illustrates this non-specificity by demonstrating the frequent occurrence of positive results with these biological tests in four common virus diseases.

Disease	Cold Agglutination	Cephalin Flocculation	Wassermann Reaction	Heterophile Agglutination
Infectious mononucleosis	+	+++	++	+++
Primary atypical pneumonia	+++	+	++	+
Lymphogranuloma venereum	+	+	+	+
Infectious hepatitis		+++	+	

\+ reported in the literature
++ common
+++ very common

SUMMARY

1. A case of lymphogranuloma venereum is reported in which a number of falsely positive laboratory tests were found.

2. Cold agglutination, Wassermann reaction, cephalin-cholesterol flocculation, and heterophilic antibody reactions are discussed from the standpoint of non-specificity.

3. The evidence supporting the view that hyperglobulinemia with abnormal globulins forms the basis for many biological tests is presented.

REFERENCES

1. Cohn, E. J., et al. Characterization of protein fractions of human plasma. *J. Clin. Investigation*, 23: 417–432, 1944.
2. Davis, B. D., Moore, D. H., Kabat, E. A. and Harris, A. Electrophoretic, ultracentrifugal and immunochemical studies on Wassermann antibody. *J. Immunol.* 50: 1–20, 1945.
3. Kabat, E. A., Hanger, F. M., Moore, D. H. and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J. Clin. Investigation*, 22: 563–568, 1943.
4. Moore, D. B., Pierson, P. S., Hanger, F. M. and Moore, D. H. Mechanism of positive cephalin-cholesterol flocculation reaction in hepatitis. *J. Clin. Investigation*, 24: 292–295, 1945.
5. Jones, C. A. and Rome, H. P. Serum proteins, Takata-Ara reaction, and liver function tests in lymphogranuloma venereum. *Am. J. Clin. Path.*, 9: 421–436, 1939.
6. Bernstein, A. Infectious mononucleosis. *Medicine*, 19: 85–159, 1940.
7. Johnson, H. H., Jr. and Burnet, F. M. Laboratory findings in lymphogranuloma inguinale. *M. J. Australia*, 1: 28–30, 1943.
8. Kampmeier, R. H., Smith, D. W. and Larsen, R. M. Blood studies in lymphogranuloma venereum; with special reference to serum proteins. *Am. J. M. Sc.*, 198: 516–528, 1939.
9. Kagan, B. M. Hyperglobulinemia. *Am. J. M. Sc.*, 206: 309–315, 1943.
10. Mann, C. H., Jr. Newer developments in clinical and laboratory aspects of lymphogranuloma venereum. *Rhode Island M. J.*, 27: 213, 1944.
11. Jeghers, H. and Selesnick, S. Hyperproteinemia: its significance. *Internat. Clin.*, 3: 248–279, 1937.
12. Stokes, J. H., Beerman, H. and Ingraham, N. R. Modern Clinical Syphilology. Philadelphia, 1945. W. B. Saunders.
13. Koteen, H. Lymphogranuloma venereum. *Medicine*, 24: 1–69, 1945.
14. Noojin, R. O., Callaway, J. L. and Schulze, W. Sulfadiazine and sulfathiazole therapy in lymphogranuloma venereum and chancroid: report of thirty cases. *Am. J. Syph., Gonor., & Ven. Dis.*, 27: 601–606, 1943.
15. Frei, W. New skin test in inguinal lymphogranuloma. *Klin. Wchnschr.*, 4: 2,148–2,149, 1925.
16. Callomon, F. T., and Brown, H. Chemotherapy of experimental lymphogranuloma venereum in mice. *Am. J. Syph., Gonor. & Ven. Dis.*, 27: 590–600, 1943.
17. Favour, C. B. Autohemagglutinins—"cold agglutinins." *J. Clin. Investigation*, 23: 891–897, 1944.
18. Stats, D. and Wassermann, L. R. Cold hemagglutination—interpretative review. *Medicine*, 22: 363–424, 1943.
19. Peterson, O. L., Ham, T. H. and Finland, M. Cold agglutinins (autohemagglutinins) in primary atypical pneumonias. *Science*, 97: 167, 1943.
20. Spingarn, C. L., Jones, J. P. and Owrutzky, B. Cold hemagglutinins in infectious mononucleosis. *U.S. Nav. M. Bull.*, 43: 717–719, 1944.
21. Straus, R. and Bernstein, M. T. Further serological studies in infectious mononucleosis. *Am. J. Clin. Path.*, 12: 174–182, 1942.
22. Wade, L. J. and Richman, E. E. Cephalin-cholesterol flocculation test. *J. Lab. & Clin. Med.*, 30: 6–13, 1945.
23. Williams, R. D. and Gutman, A. B. Hyperproteinemia with reversal of albumin:globulin ratio in lymphogranuloma inguinale. *Proc. Soc. Exper. Biol. & Med.*, 34: 91–94, 1936.

Juvenile Diabetes as a Sequel to Mumps*

HOWARD U. KREMER, M.D.

PHILADELPHIA, PENNSYLVANIA

In a recent review of the literature it was noted that the usual complications of mumps cited were orchitis, nephritis, encephalitis and more recently, myocarditis.[1] However, there was no mention made of diabetes mellitus as a sequel of this disease. Pancreatitis was mentioned as a complication of mumps, and this was associated with the familiar symptoms of acute abdominal pain, vomiting, and a picture of acute abdominal catastrophe, but there was no reference to any patients with an acute onset of hyperglycemia or glycosuria.

The occurrence in two patients of diabetes in which mumps appeared to play a part in the etiology would therefore seem to merit consideration.

CASE REPORTS

CASE I. The patient was a fifteen year old white male who six weeks before his admission to the hospital was ill with the mumps and was confined to bed for three weeks. He then noted nocturia and frequency. He drank a great deal of soda during the day and had an increased appetite for food. He had lost weight since the onset of his illness.

He had a past medical history of measles, pertussis and varicella. Tonsillectomy had been performed in July, 1945. The family history was negative for diabetes. The physical examination was negative. The fasting blood sugar was 165 mg. per cent. Urinalysis showed sugar, four plus. The patient was put on a diet of P-80, F-80 and CHO-135. The insulin dosage was determined at 10P-0-10P. The blood sugar on discharge was 85 mg. per cent and the urine was free of sugar.

CASE II. The patient was an eleven year old white male who was first admitted to the hospital in November, 1942, because of polydypsia and polyuria. One month before admission the patient began to drink a great deal of water and to pass more urine. He also had had a cold for the past month.

The past medical history included pneumonia, tonsillectomy and whooping cough. He had had mumps about six weeks before admission. Physical examination was negative. The urinalysis revealed sugar four plus, and the blood sugar was 200 mg. per cent. He was standardized at the hospital and was put on a diet of P-75, F-100 and CHO-125. The insulin dosage was 15P-0-10P. On November 18, 1942, the patient had a slight insulin shock and the insulin was reduced to 15P-0-10P from 20P-0-15P. He remained so standardized and continued to do well until June 28, 1943, when he was admitted to the hospital with scarlet fever. He ran a blood sugar of 68–296 mg. per cent. He went to the seashore to convalesce and his weight increased from 73 to 78 pounds. The blood sugar in September, 1943, was 150 and he was given 15P plus 5-0-10. In November, 1943, the blood sugar was 350 mg. per cent and the urine sugar was four plus. Insulin dosage was 15-P-10-10P. In December, 1943, the insulin was 20P plus 5-0-10. In January, 1944, the sugar in his urine was negative for three days, and the blood sugar was 180. The insulin was then 20P plus 5-0-10P. He continued to gain weight. In June, 1944, the blood sugar was 235 mg. per cent two hours after breakfast. He had an episode of acidosis on July 28, 1944, and he was given 30P-7-0-5. By the end of 1944, he weighed 96¾ pounds. In October, 1945, he had an attack of gastroenteritis which upset his regulation. His weight in June, 1946, was 108 pounds and the blood sugar was 380. Insulin

* From The Doctors' Hospital of Philadelphia, Philadelphia, Pa.

3. The evidence supporting the view that hyperglobulinemia with abnormal globulins forms the basis for many biological tests is presented.

REFERENCES

1. Cohn, E. J., et al. Characterization of protein fractions of human plasma. *J. Clin. Investigation*, 23: 417–432, 1944.
2. Davis, B. D., Moore, D. H., Kabat, E. A. and Harris, A. Electrophoretic, ultracentrifugal and immunochemical studies on Wassermann antibody. *J. Immunol.* 50: 1–20, 1945.
3. Kabat, E. A., Hanger, F. M., Moore, D. H. and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J. Clin. Investigation*, 22: 563–568, 1943.
4. Moore, D. B., Pierson, P. S., Hanger, F. M. and Moore, D. H. Mechanism of positive cephalin-cholesterol flocculation reaction in hepatitis. *J. Clin. Investigation*, 24: 292–295, 1945.
5. Jones, C. A. and Rome, H. P. Serum proteins, Takata-Ara reaction, and liver function tests in lymphogranuloma venereum. *Am. J. Clin. Path.*, 9: 421–436, 1939.
6. Bernstein, A. Infectious mononucleosis. *Medicine*, 19: 85–159, 1940.
7. Johnson, H. H., Jr. and Burnet, F. M. Laboratory findings in lymphogranuloma inguinale. *M. J. Australia*, 1: 28–30, 1943.
8. Kampmeier, R. H., Smith, D. W. and Larsen, R. M. Blood studies in lymphogranuloma venereum; with special reference to serum proteins. *Am. J. M. Sc.*, 198: 516–528, 1939.
9. Kagan, B. M. Hyperglobulinemia. *Am. J. M. Sc.*, 206: 309–315, 1943.
10. Mann, C. H., Jr. Newer developments in clinical and laboratory aspects of lymphogranuloma venereum. *Rhode Island M. J.*, 27: 213, 1944.
11. Jeghers, H. and Sallenger, S. Hyperproteinemia: its significance. *Internat. Clin.*, 3: 248–279, 1937.
12. Stokes, J. H., Beerman, H. and Ingraham, N. R. Modern Clinical Syphilology. Philadelphia, 1945. W. B. Saunders.
13. Koteen, H. Lymphogranuloma venereum. *Medicine*, 24: 1–69, 1945.
14. Noojin, R. O., Callaway, J. L. and Schulze, W. Sulfadiazine and sulfathiazole therapy in lymphogranuloma venereum and chancroid: report of thirty cases. *Am. J. Syph., Gonor., & Ven. Dis.*, 27: 601–606, 1943.
15. Frei, W. New skin test in inguinal lymphogranuloma. *Klin. Wchnschr.*, 4: 2,148–2,149, 1925.
16. Callomon, F. T., and Brown, H. Chemotherapy of experimental lymphogranuloma venereum in mice. *Am. J. Syph., Gonor. & Ven. Dis.*, 27: 590–600, 1943.
17. Favour, C. B. Autohemagglutinins—"cold agglutinins." *J. Clin. Investigation*, 23: 891–897, 1944.
18. Stats, D. and Wassermann, L. R. Cold hemagglutination—interpretative review. *Medicine*, 22: 363–424, 1943.
19. Peterson, O. L., Ham, T. H. and Finland, M. Cold agglutinins (autohemagglutinins) in primary atypical pneumonias. *Science*, 97: 167, 1943.
20. Spingarn, C. L., Jones, J. P. and Owrutzky, B. Cold hemagglutinins in infectious mononucleosis. *U.S. Nav. M. Bull.*, 43: 717–719, 1944.
21. Straus, R. and Bernstein, M. T. Further serological studies in infectious mononucleosis. *Am. J. Clin. Path.*, 12: 174–182, 1942.
22. Wade, L. J. and Richman, E. E. Cephalin-cholesterol flocculation test. *J. Lab. & Clin. Med.*, 30: 6–13, 1945.
23. Williams, R. D. and Gutman, A. B. Hyperproteinemia with reversal of albumin:globulin ratio in lymphogranuloma inguinale. *Proc. Soc. Exper. Biol. & Med.*, 34: 91–94, 1936.

Juvenile Diabetes as a Sequel to Mumps*

HOWARD U. KREMER, M.D.

PHILADELPHIA, PENNSYLVANIA

In a recent review of the literature it was noted that the usual complications of mumps cited were orchitis, nephritis, encephalitis and more recently, myocarditis.[1] However, there was no mention made of diabetes mellitus as a sequel of this disease. Pancreatitis was mentioned as a complication of mumps, and this was associated with the familiar symptoms of acute abdominal pain, vomiting, and a picture of acute abdominal catastrophe, but there was no reference to any patients with an acute onset of hyperglycemia or glycosuria.

The occurrence in two patients of diabetes in which mumps appeared to play a part in the etiology would therefore seem to merit consideration.

CASE REPORTS

CASE I. The patient was a fifteen year old white male who six weeks before his admission to the hospital was ill with the mumps and was confined to bed for three weeks. He then noted nocturia and frequency. He drank a great deal of soda during the day and had an increased appetite for food. He had lost weight since the onset of his illness.

He had a past medical history of measles, pertussis and varicella. Tonsillectomy had been performed in July, 1945. The family history was negative for diabetes. The physical examination was negative. The fasting blood sugar was 165 mg. per cent. Urinalysis showed sugar, four plus. The patient was put on a diet of P-80, F-80 and CHO-135. The insulin dosage was determined at 10P-0-10P. The blood sugar on discharge was 85 mg. per cent and the urine was free of sugar.

CASE II. The patient was an eleven year old white male who was first admitted to the hospital in November, 1942, because of polydypsia and polyuria. One month before admission the patient began to drink a great deal of water and to pass more urine. He also had had a cold for the past month.

The past medical history included pneumonia, tonsillectomy and whooping cough. He had had mumps about six weeks before admission. Physical examination was negative. The urinalysis revealed sugar four plus, and the blood sugar was 200 mg. per cent. He was standardized at the hospital and was put on a diet of P-75, F-100 and CHO-125. The insulin dosage was 15P-0-10P. On November 18, 1942, the patient had a slight insulin shock and the insulin was reduced to 15P-0-10P from 20P-0-15P. He remained so standardized and continued to do well until June 28, 1943, when he was admitted to the hospital with scarlet fever. He ran a blood sugar of 68–296 mg. per cent. He went to the seashore to convalesce and his weight increased from 73 to 78 pounds. The blood sugar in September, 1943, was 150 and he was given 15P plus 5-0-10. In November, 1943, the blood sugar was 350 mg. per cent and the urine sugar was four plus. Insulin dosage was 15-P-10-10P. In December, 1943, the insulin was 20P plus 5-0-10. In January, 1944, the sugar in his urine was negative for three days, and the blood sugar was 180. The insulin was then 20P plus 5-0-10P. He continued to gain weight. In June, 1944, the blood sugar was 235 mg. per cent two hours after breakfast. He had an episode of acidosis on July 28, 1944, and he was given 30P-7-0-5. By the end of 1944, he weighed 96¾ pounds. In October, 1945, he had an attack of gastroenteritis which upset his regulation. His weight in June, 1946, was 108 pounds and the blood sugar was 380. Insulin

* From The Doctors' Hospital of Philadelphia, Philadelphia, Pa.

dose was set at 30P plus 10-0-10 and the patient has been faring well ever since then.

COMMENT

The chronologic sequence of events in the two reported case histories permits us to surmise that there may have been a causal relationship between the occurrence of mumps and the onset of overt diabetes mellitus. The four-year course in the second patient certainly suggested that the condition had become well established. Interestingly enough, as in most juvenile diabetics, the management of the patient was difficult as indicated by the frequent change in the insulin regimen.

CONCLUSIONS

Two patients with diabetes mellitus in whom epidemic parotitis probably was a causative factor have been presented. No symptoms of diabetes antedated the attack of mumps in either case. Unfortunately no data are available as to glycosuria or hyperglycemia before or during the course of mumps; however, the clinical course following mumps suggests that this virus disease might have been a causative factor, possibly as the result of concomitant involvement of the pancreas.

REFERENCE

1. Rosenberg, David H. Acute myocarditis in mumps. *Arch. Int. Med.*, 76: 257, 1945.

new

improved

limited

HYDRYLLIN

This new product of Searle Research is composed of a synthetic histamine antagonist, diphenhydramine*, and the well accepted bronchial antispasmodic, Aminophyllin. The combining of these two components provides an augmented effect in the prevention and control of allergic disturbances associated with abnormal histamine release, with limited disagreeable side reactions.

Each tablet contains:
Diphenhydramine* (Searle)..... 25 mg.
Aminophyllin (Searle).....100 mg.

Indicated in:
Urticaria, atopic dermatitis, eczematous dermatitis, penicillin reactions, hay fever, allergic rhinitis complicated by bronchial asthma, bronchial asthma, other allergic manifestations.

Recommended dosage:
One or two tablets three or four times a day.

Now available at your prescription pharmacy in bottles of 100 tablets. A product of G. D. Searle & Co., Chicago 80, Illinois.

*Diphenhydramine is the name adopted by the Council on Pharmacy and Chemistry of the American Medical Association for β-dimethylaminoethyl benzohydryl ether.

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE

BRISTOL Penicillin in Oil and Wax is now

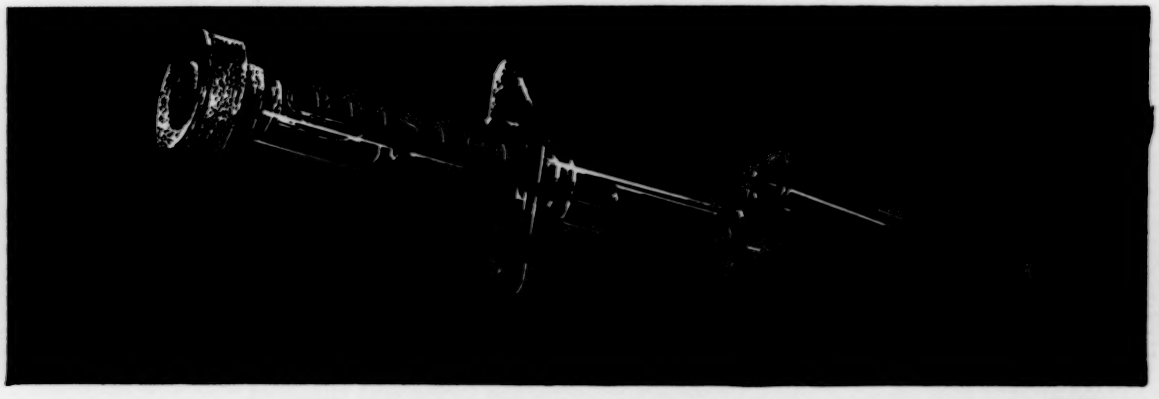
LIQUID

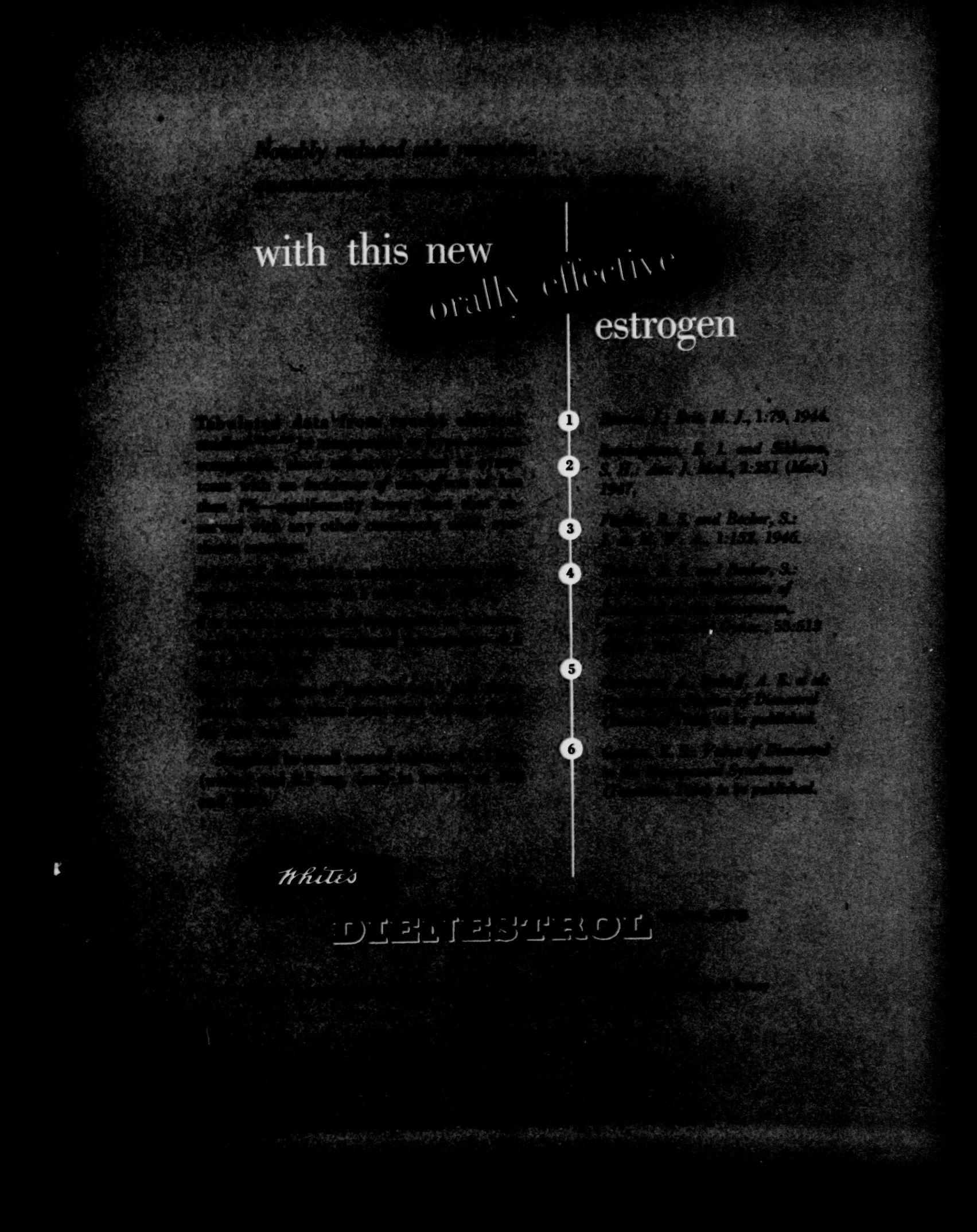
. . . for easier administration

Now you can inject Bristol's Crystalline Sodium Penicillin G in Oil and Wax (Romansky Formula) with far greater ease than in the past. Due entirely to changes in the manufacturing process and without any alteration in formula, the viscosity of the product at room temperature has been brought to a point which approximates that of U.S.P. glycerin. This is a significant development in penicillin therapy. Specify Bristol and obtain the benefits of LIQUID Romansky Formula.

Supplied in one cc. cartridges of 300,000 units, with or without special syringe equipment, and in 10 cc. rubber-stoppered vials. Needs no refrigeration in storage or warming before use.

Bristol LABORATORIES INC., SYRACUSE, NEW YORK




with this new
orally effective
estrogen
1
2
3
4
5
6
White's
DIELESTROL

SYSTEMIC REHABILITATION

A **ROERIG** *Preparation*

Gainful occupation restored

For long-lasting alleviation of pain and restoration of function in arthritic patients, systemic rehabilitation has been found to be the most rational therapeutic regimen.

Darthronol is widely accepted as an important therapeutic factor in the systemic rehabilitation of the arthritic. The beneficial antiarthritic effects of the contained massive dosage of vitamin D, the improvement of appetite, decrease of pain, restoration of normal digestive function and general well-being—which so frequently follow adequate dosage of Darthronol—all tend to hasten recovery and make possible the return to a gainful occupation.

For the Arthritic

DARTHRONOL

J. B. ROERIG AND COMPANY • 536 Lake Shore Drive • Chicago 11, Illinois

Ever wish you were Aladdin?

You remember him . . .

He was the lucky fellow who found a magic lamp. It gave him everything he wished for—from diamond-crusted palaces to a sultan's daughter as his bride.

You've probably wished a lot of times for a miracle like this to happen to you. Maybe not for out-of-this-world treasures, but for something that will take care of the things that are bound to come up.

Like medical expenses, or college for the kids. Or maybe just for the nice, safe feeling it gives you to have some extra money put aside for the future.

Though no magic is involved, there is a way to give you this security. The Payroll Savings Plan. Or, if you're not eligible for the Payroll Plan but have a checking account, the new Bond-a-Month Plan.

Either way, it's almost unbelievable how quickly your money accumulates.

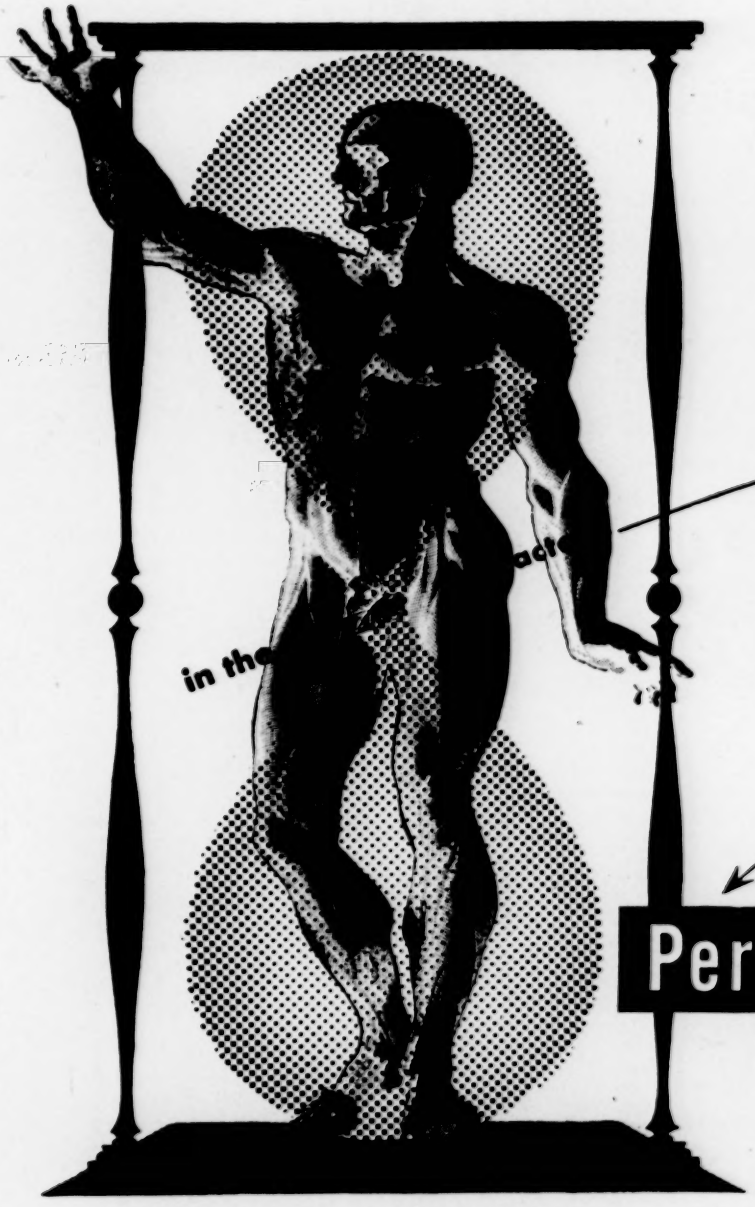
Where else can you get such a *safe*, generous return on your money ($4 for every $3)? It's so simple—so easy, you hardly miss the money that you're saving.

And don't forget—at the same time, you're *making more*!

Next to a magic lamp, there's no better way than this to make sure your future is secure.

Save the easy, automatic way . . . with U.S. Savings Bonds

Contributed by this magazine in co-operation with the Magazine Publishers of America as a public service.



Perandren

As time runs out, Perandren is specific in the treatment of the male climacteric. Perandren IS testosterone propionate, the most potent androgen available for intramuscular administration.

PERANDREN . . . T. M. Reg. U. S. Pat. Off.

For further information, write Professional Service Department.

CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.

Eliminate infection in

WOUNDS ULCERS
LESIONS FISSURES
ABSCESSES CYSTS

by simple topical application

Glycerite of Hydrogen Peroxide ipc

[illegible] selective,

[illegible] the mechanical advantages of liquid [illegible] types of medication

[illegible] penetrates into and [illegible] from deeper parts of wounds, [illegible] particulate matter to the surface

[illegible] of healthy tissue and [illegible]

[illegible]

[illegible]

Bibliography

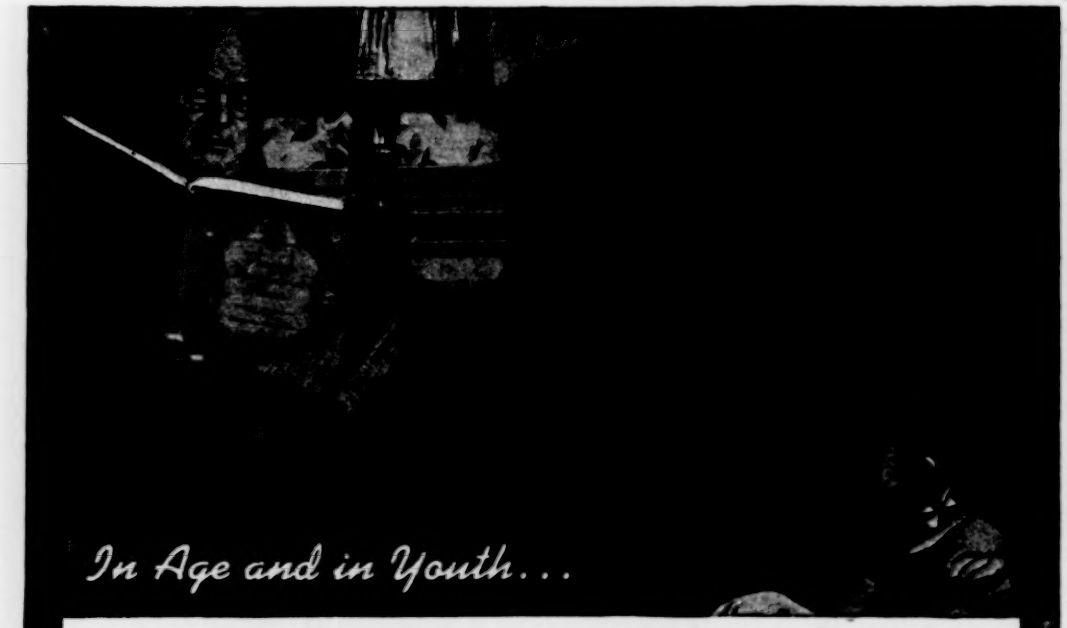
[illegible]

GLYCERITE OF HYDROGEN PEROXIDE *ipc*

CONSTITUENTS:
Hydrogen peroxide (90%) 2.5%
8-Hydroxyquinoline 0.1%
Especially prepared glycerol qs. ad. 120cc.
Supplied in four-ounce bottles

International PHARMACEUTICAL CORPORATION

132 Newbury Street, Boston 16, Massachusetts



In Age and in Youth...

MANDELAMINE

Reg. U. S. Pat. Off.
(Methenamine Mandelate)

IS AN ESPECIALLY EFFECTIVE URINARY ANTISEPTIC

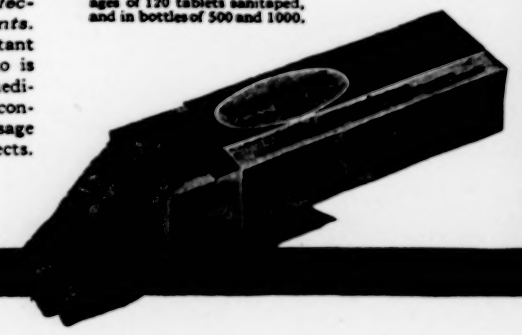
Safety, ease of administration, and characteristically prompt action combine to make Mandelamine an especially efficient agent in the treatment of urinary infections in children and in elderly patients.

Freedom from drug toxicity is an important consideration to the busy physician who is unable to maintain patients under close medical supervision. Mandelamine may be confidently prescribed in therapeutic dosage virtually without consideration of toxic effects.

Uncomplicated oral administration of Mandelamine requires no supplementary acidification, restriction of fluid intake, dietary control, or other special measures. Only in those infections due to urea-splitting organisms, may accessory acidification be necessary.

Early control of common urinary infections is the characteristic response to Mandelamine therapy. Disturbing urinary symptoms are usually alleviated rapidly and, in the absence of obstruction, the urine is promptly cleared of organisms in a high percentage of cases.

Mandelamine is supplied in enteric coated tablets of 0.25 Gm. (3¾ grains) each, in packages of 120 tablets sanitaped, and in bottles of 500 and 1000.



NEPERA CHEMICAL CO. INC,
21 Gray Oaks Ave.
Yonkers 2, New York
Please send me literature, and a physician's sample of Mandelamine.

Name.....M.D.

Street.....

City.....State.....

NEPERA CHEMICAL CO. INC.

Manufacturing Chemists Yonkers 2, New York